COMPARATIVE STUDIES ON EFFERVESCENT AND NON-EFFERVESCENT FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT

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Submitted By
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MAY-2018

CERTIFICATE

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This is to certify that the dissertation entitled **" COMPARATIVE STUDIES ON EFFERVESCENT AND NON-EFFERVESCENT FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT "** is a bonafide work done by **Ms. T.NITHYA (Reg.No:261611305), Department of Pharmaceutics, College of Pharmacy, Madurai Medical College** in partial fulfillment of The Tamil Nadu Dr.M.G.R Medical University rules and regulations for award of **MASTER OF PHARMACY IN PHARMACEUTICS** under my guidance and supervision during the academic year 2017–2018.

Name & Signature of the Guide

Name & Signature of the Head of Department

Name & Signature of the Dean/Principal

ACKNOWLEDGEMENT

ACKNOWLEDGEMENT

Lives of great men all remind us
We can make our lives sublime
And departing leave behind us
Foot prints on the sands of time"

First of all, I bow before the Sovereign Almighty by the grace of whom I have been able to successfully complete my project.

I humbly present this work to the external ALMIGHTY. Indeed my project is a small work done with the help of primitive persons at heart so it is my bounded duty to promulgate them individually.

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Place: **(T.NITHYA)**

Date:

CONTENTS

LIST OF ABBREVIATIONS USED

Abs.	Absorbance
Amt.	Amount
AR/LR	Analytical Reagent/ Laboratory Reagent
AUC	Area under the curve
BDDS	Bioadhesive drug delivery systems
C_{max}	Peak concentration
CDR	Cumulative drug release
CLA	Cumulative loss added
CDDS	Controlled drug delivery systems
DDS	Drug delivery system
DSC	Differential Scanning Calorimetry
ºC	Degree Centigrade
FDDS	Floating drug delivery system
FLT	Floating lag time
FT-IR	Fourier Transform Infrared spectroscopy
GET	Gastric emptying time
GRDF	Gastro-retentive dosage form
GRDDS	Gastro-retentive drug delivery system
GIT	Gastrointestinal tract
HBS	Hydrodynamically balanced system
HPMC	Hydroxy propyl methylcellulose
ICH	International Conference for Harmonization
K_E	Elimination rate constant
MCC	Microcrystalline cellulose
MMC	Migrating Myloelectric Cycle
NSAIDS	Non steroidal anti inflammatory drugs

PEG	Poly ethylene glycol
PVA	Poly vinyl alcohol
PVP	Poly vinyl pyrolidone
Q6	Drug release after 6 h
Q12	Drug release after 12 h
RPM	Revolution per minute
% RH	Percentage relative humidity
SD	Standard deviation
SS	Stock solution
$t_{1/2}$	Elimination half-life
$t_{50\%}$	Time required to 50% of drug
UV	Ultraviolet
WHO	World Health Organization

CHAPTER I

INTRODUCTION

INTRODUCTION

For decades an acute condition or chronic illness is being clinically treated through delivery of drugs to the patients in form of some pharmaceutical dosage forms like tablets, capsules, creams, liquids, ointments, aerosols, etc.

To attain and maintain the concentration of an administered drug within therapeutically effective range, it is often required to take drug dosage several times and this result in a fluctuating drug level in plasma. Controlled or sustained drug delivery systems have been introduce to overwhelm the problem of fluctuating drug levels related with conventional dosage forms **(Vyas.S.P & Khar, 2002)** , **(Jaiswal.S.B *et al*., 2007). (Figure 1.)**

Fundamentally, there are three modes of drug delivery which are,

- **SUSTAINED RELEASE DRUG DELIVERY SYSTEM**
- **CONTROLLED RELEASE DRUG DELIVERY SYSTEM**
- **TARGETED DRUG DELIVERY SYSTEMS**

CONVENTIONAL DRUG DELIVERY SYSTEM

Conventional drug delivery system is known to provide a prompt release of drug; therefore, to attain as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take these types of drug delivery system several times a day. This result in a significant fluctuation in drug levels **(Chien Y.W, 1982; Jaiswal.S.B *et al*., 2007).**

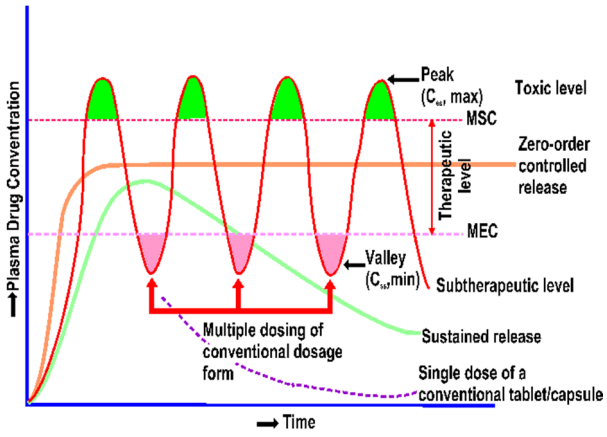


Figure 1(a): Plasma drug concentration-time profile for conventional dosage

Drawbacks of Conventional Dosage Forms:

- Poor patient compliance
- Increased chances of missing the dose of a drug
- Shorter half life
- To attain steady-state plasma concentration is difficult.
- Fluctuations in drug levels **(Shalin A. Modi *et al*., 2011; Chien Y.W, 1992).**

A) SUSTAINED RELEASE DRUG DELIVERY

Sustained release drug delivery system, which means the release of active agent is slower than any conventional formulation, but is significantly affected by an external environment. The onset of its pharmacological action is delayed, and the duration of therapeutic effect is sustained. That means, to retard the release of a therapeutic agent in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained **(Jaiswal.S.B *et al*., 2007; Shalin A. Modi *et al*., 2011).**

B) CONTROLLED RELEASE DRUG DELIVERY SYSTEM

Controlled release systems provide a release profile independent of external environment and predominantly controlled by the design of the system. It implies

a predictability and reproducibility in the drug release kinetics. That means, the release of drug ingredient(s) from a controlled-release drug delivery system proceeds at a rate profile that is predictable kinetically, and also reproducible from one unit to another **(Xiaoling Li *et al*., 2005; Brahmankar D.M *et al*., 1995).** The plasma level of drug should be maintained within the safe margin and effective range, for this proper and calculated dose of the drug need to be given at different time intervals by conventional dosage forms **(Shalin A. Modi *et al*., 2011).**

C) TARGETED DRUG DELIVERY SYSTEM

Targeted delivery refers to the systemic administration of a drug carrier with the goal of delivering the drug to specific cell types, tissues, or organs.

The distribution of other tissues seems unnecessary, and a potential cause of toxicity. Most of diseases treated by cytotoxic agents not only demand for controlled drug delivery but also the pattern of delivery is directed to be specific, precise and defined at quantitative levels.

Approaches are being adopted either to control the distribution of drug by incorporating it in a carrier or altering the structure of the drug at the molecular level, or by controlling the input of the drug into the bioenvironmental to ensure a programmed and desirable biodistribution **(Vyas.S.P & Khar, 2002).**

RATIONALE OF SUSTAINED, CONTROLLED AND TARGETED DRUG DELIVERY:

The drug delivery system are usually known by terms like sustained, controlled, targeted, novel, and therapeutic and programmed. However, the basic rationale for these varied delivery modules is the alteration or manipulation of

pharmacokinetic and pharmacodynamic of pharmacologically active moieties. This can be achieved either by using novel delivery devices (like Liposome, Transdermal patches or Matrix or Membrane controlled devices) , or by modifying the structure in molecular level (Prodrug or Chemical delivery system) and/or physiological parameters inherent by route of administration selected (like rectal route to avoid first pass metabolism). A drug delivery system may be thought of as one in which three components are included: the drug input function: the pharmacokinetic responses (metabolism): and the pharmacodynamic responses (therapeutic and side effects) **(Xiaoling Li *et al*., 2005; Brahmankar D.M *et al*., 2002).**

It is important to critically evaluate different terms used under broad category of novel drug delivery systems:

- Sustained or controlled drug delivery systems provide drug action at a predetermined rate by providing a prolonged or constant (zero-order) release respectively, at therapeutically effective levels in the circulation.
- Localized drug delivery devices through spatial or temporal control of drug release (usually rate-limiting) in the vicinity of the target.
- Rate-preprogrammed drug delivery systems, by the release of drug molecules by system design, which controls the molecular diffusion of drug molecules. Fick's laws of diffusion are followed.
- Targeted drug delivery by using carriers either meant for passive preprogrammed or active preprogrammed or self-programmed approach or usually appended with suitable site-directing molecules which recognize their receptor or carbohydrate determinants at the target.

RECENT DEVELOPMENTS

Controlled-released formulations have been widely developed and marketed over the past 30years under various terms such as sustained release, prolonged-release, timed-release, or other similar names that are often ill-defined and misleading.

Recently, a number of novel drug delivery systems that uses unique concepts have been studied intensively. Some of the strategies include targeted delivery, self-regulated release, biofeedback mechanisms, and drug attached to biological carriers **(Vyas.S.P & Khar, 2002; Xiaoling Li *et al.,* 2005).**

Controlled-release formulations can be designed for any route of administrations as follows:

- Oral
- Parenteral
- Implants
- Transdermal
- Other routes: ocular, nasal, vaginal, etc.

Reasons for Interest in New DDS

- ❖ Improving conventional dosage forms
- ❖ Exclusivity for existing drugs
- ❖ High cost for developing new drugs
- ❖ Delivery of bioengineered compounds
- ❖ Enhanced efficacy and safety

Some of the potential benefits and drawbacks of controlled-release and novel drug delivery systems are as follows:

Potential Benefits of Novel Drug Delivery System

- Convenience in dosing
- Higher patient compliance
- Better utilization of drugs
- Reduced adverse effects
- Improved efficacy

Potential Problems of Novel Drug Delivery

- Delivery of drugs to the target tissues/organs
- Extravasations of drugs/carriers in the tissues/organs
- Liberation of drugs from the carrier
- Penetration into specific cells/cell components
- Control of residence time at the receptor site.

ORAL CONTROLLED RELEASE FORMULATIONS

Oral route has been the commonly selected and most suitable for the drug delivery. Oral route of administration has more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than other routes of drug delivery **(Stanley S.Davies *et al*., 2005; Shalin A. Modi *et al*., 2011).**

The oral controlled drug delivery systems are mostly solids and based on diffusion, dissolution or combination of both mechanisms in the control of release rate of drug.

Novel oral drug delivery systems are broadly classified into two categories as they may control release dosage forms as well as targeting dosage forms. General controlled manner in the GIT for systemic uptake and no particular area

of GIT specified. In contrast, targeted preparations are releasing the drug in a specified area or tissue of the GI (e.g. floating drug delivery system).

Targeting systems are either releasing drug in controlled manner or in one burst at the specific area. The goal of a targeted oral drug delivery system (TODDS) is to achieve better therapeutics success compared to conventional dosage form. This can be achieved by improving the pharmacokinetic profile, patient convenience and compliance in therapy (Stanley S.Davies *et al*., 2005).

Advantages of TODDS

- Reduced dosing frequency
- Better patient convenience and compliance
- Reduced GI side effects and other toxic effects.
- Less fluctuating plasma drug level
- More uniform drug effect
- Less total dose
- Better stability of the drug **(Brahmankar D.M *et al*., 1995; Vyas S.P & Khar, 2002).**

Disadvantages of TODDS:

- Higher cost
- Relatively poor *in vitro-in vivo* correlation
- Possible dose dumping
- Reduced potential for dose change or withdrawal in the event of toxicity **(Brahmankar D.M *et al*., 1995).**

Targeting of drugs through oral route involves control of time of release or location of release. On the basis of environmental, anatomical and physiological factors these drug delivery system can be classified with respect to target site as follows:

- Systems targeted to stomach/duodenum
- Systems targeted to small intestine
- Systems targeted to large intestine/colon
- Systems targeted to lymphatic.

Classification of oral controlled drug delivery system

1. Continuous release system

- Dissolution controlled release system
- Diffusion controlled release system
- Diffusion and dissolution controlled release system.
- Ion exchange resin drug complexes
- Slow dissolving salt and complexes
- pH independent formulations.
- Osmotic pressure controlled systems
- Hydrodynamic pressure controlled systems.

2. Delayed transit and continuous release systems

- Altered density system.
- Mucoadhesive system.
- Size based systems.

3. **Delayed Release system**

- Intestinal release system.
- Colonic release system.

Advantages of controlled drug delivery systems

- Improved patient convenience and compliance
- Reduction in fluctuation in steady state levels.
- Increased safety margin of high potency drugs.
- Reduced GI side effects.
- Reduced dosing frequency.
- Better patient acceptance and compliance.
- Less fluctuation at plasma drug levels.
- Dose dumping.
- Need of additional patient education **(Jain N.K, 2002; Vyas S.P & Khar, 2002).**

Disadvantages of controlled drug delivery systems

- Decreased systemic availability.
- Poor *invitro-in vivo* correlations.
- Chances of dose dumping.
- Dose withdrawal is not possible.
- Higher cost of formulation.

CHAPTER 2

GRDDS- A REVIEW

GASTRO RETENTIVE DRUG DELIVERY SYSTEM- REVIEW

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity **(Amit Kumar Nayak *et al.,* 2010).**

To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT).

These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment. Also

prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine (e.g. treatment of peptic ulcer, etc) **(Amit Kumar Nayak *et al.,* 2010).**

BIOLOGICAL ASPECTS OF GRDDs

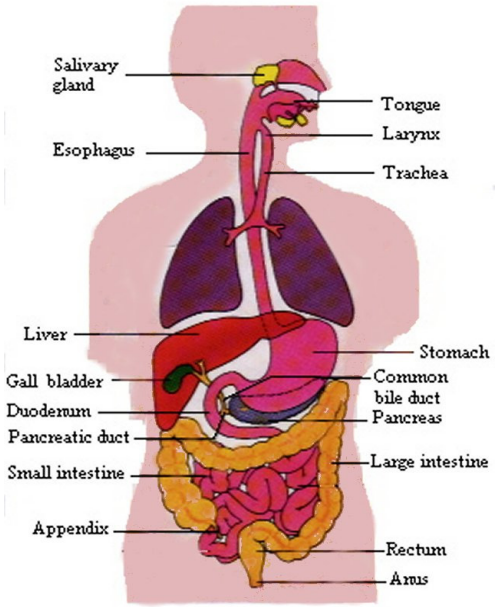
Anatomy of the gastrointestinal tract:

The gastrointestinal tract is divided into three main regions namely:

- Stomach.
- Small intestine (Duodenum, Jejunum and lieum).
- Large intestine.

The GIT is a muscul ar tube, from the mouth to the anus, which f unctions to take in nutrients and eliminate waste by secretion, motility, digestion, absorption and excretion, which are known as physiological processes **(Shiv Kumar Yadav *et al*., 2011).**

Figure 2(a): Anatomy of Gastro Intestinal Tract



Basic gastrointestinal tract physiology:

The stomach is an expanded section of the digestive tube between the oesophagus and small intestine. The wall of the stomach is structurally similar to th e other parts of the digestive tube, with the exception that stomach has an extra, obliq ue layer of smooth muscle inside the circular layer, which aids in the performance of complex grinding motions. In the empty state, the stomach is contracted and its mucosa and sub mucosa are thrown up into distinct folds called rugae **(Natasha Sharma *et al*., 2011).** The stomach is anatomically divided into three parts,

- Fundus
- Body
- Antrum (or pylorus).

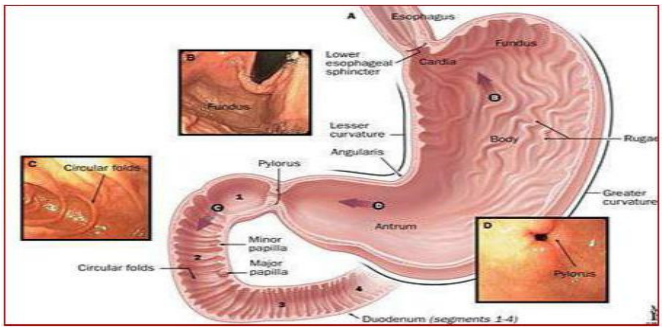


Figure 2(b) : Physiology of stomach

The proximal stomach, made up of the fundus and body regions, serves as a reservoir for ingested materials while the distal region (antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington (Neha Narang *et al*., 2011).

Figure 2(c) : Schematic representation of Interdigestive Motility

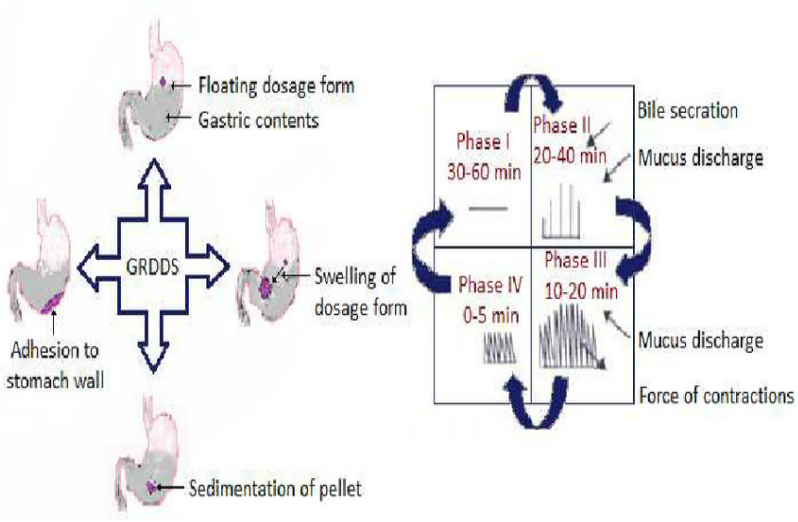


Table 2(a): Four phases in migrating myoelectric complex (MMC)

(Shweta Arora *et al*., 2005)

PHASES	
PHASE I	It is a quiescent period lasting from 30 to 60 minutes with no contractions.
PHASE II	It consists of intermittent contractions that gradually increase in intensity as the phase progresses, and it lasts about 20 to 40 minutes. Gastric discharge of fluid and very small particles begins later in this phase.
PHASE III	This is a short period of intense distal and proximal gastric contractions (4–5 contractions per minute) lasting about 10 to 20 minutes; these contractions, also known as ‘‘House-keeper wave,’’ sweep gastric contents down the small Intestine.
PHASE IV	This is a short transitory period of about 0 to 5minutes, and the contractions dissipate between the last part of phase III and quiescence of phase I.

Need for gastroretention

- Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).
- Drugs that are less soluble or that degrade at the alkaline pH.
- Drugs that are absorbed due to variable gastric emptying time.
- Local or sustained drug delivery to the stomach and proximal small intestine to treat certain conditions.
- Treatment of peptic ulcers caused by H.Pylori infections **(Amit Kumar Nayak *et al*., 2010).**

POTENTIAL DRUG CANDIDATES FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

- Drugs those are locally active in the stomach.
- Drugs that have narrow absorption window in gastrointestinal tract (GIT)
- Drugs those are unstable in the intestinal or colonic environment
- Drugs that disturb normal colonic microbes
- Drugs that exhibit low solubility at high pH values **(Amit Kumar Nayak *et al*., 2010)**

DRUGS THOSE ARE UNSUITABLE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

- Drugs that have very limited acid solubility e.g. Phenytoin etc.
- Drugs that suffer instability in the gastric environment e.g. Erythromycin etc.
- Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc **(Amit Kumar Nayak *et al*., 2010).**

Formulation aspects for GRDDS

- It must be effective retention in the stomach to suit for the clinical demand.
- It must be convenient for intake to facilitate patient compliance.
- It must have sufficient drug loading capacity and control drug release profile.
- It must have full degradation and evacuation of the system once the drug release is over.
- It should not have effect on gastric motility including emptying pattern.
- It should not have other local adverse effects **(Vinod K.R. *et al.,* 2010)**

Factors affecting gastric retention

The gastric retention time (GRT) of dosage form is controlled by several factors that affect their efficacy as a gastro retentive system **(Vinod K.R. *et al.,* 2010; Vaishali Sharma *et al*., 2011).**

1. **Density:** Gastric retention time (GRT) is a function of buoyancy of dosage form that is dependent on the density.
2. **Size:** Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.
3. **Shape:** Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.
4. **Single or Multiple unit formulation:** Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

5. **pH (Hydrogen Ion Concentration)** – The mean pH (+ S.D.) along the G.I. Tract in normal subjects are given by:

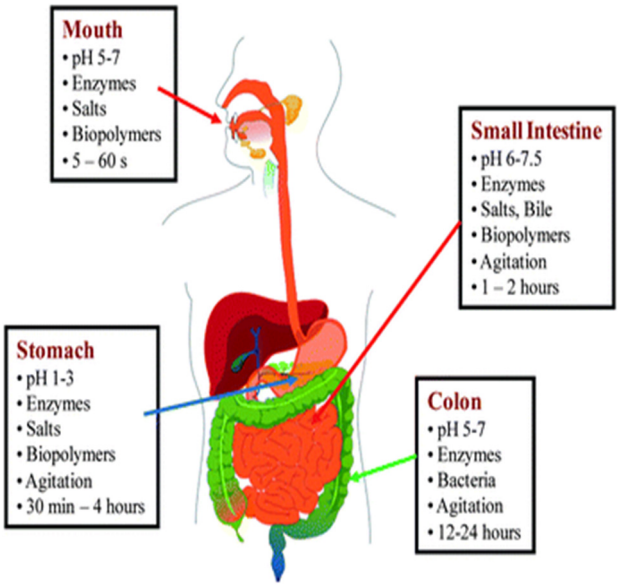


Figure 2(d) : pH of Gastro Intestinal Tract

6. **Fed or unfed state:** Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2hrs. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

7. **Nature of meal:** Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

8. **Caloric content:** GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.

9. **Frequency of feed:** The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
10. **Gender:** Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.
11. **Age:** Elderly people, especially those over 70, have a significantly longer GRT.
12. **Posture:** GRT can vary between supine and upright ambulatory states of the patient.
13. **Concomitant drug administration:** Anticholinergics like atropine, propantheline, opiates like codeine and prokinetic agents like Metoclopramide and Cisapride, can affect floating time.
14. **Biological factors:** Diabetes and Crohn's disease etc.

Approaches to Gastric retention

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These systems include **(Vinod K.R. *et al.,* 2010; Vaishali Sharma *et al*., 2011),**

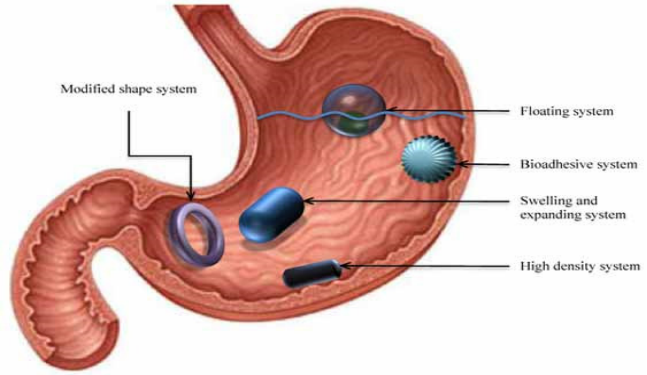


Figure 2(e): *In vivo* picturisation of various gastro retentive formulations

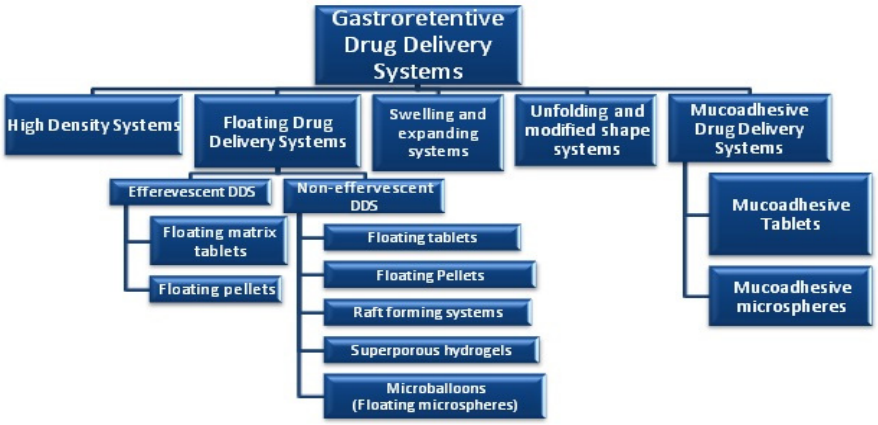


Figure 2(f): Schematic representation of various Gastro retentive formulations

1. **High density (sinking) system or non- floating drug delivery system:**

This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~ 1.004 gm/cm^3). These formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc. The materials increase density by up to 1.5- 2.4 gm/cm^3. **(Amit Kumar Nayak *et al*., 2010).**

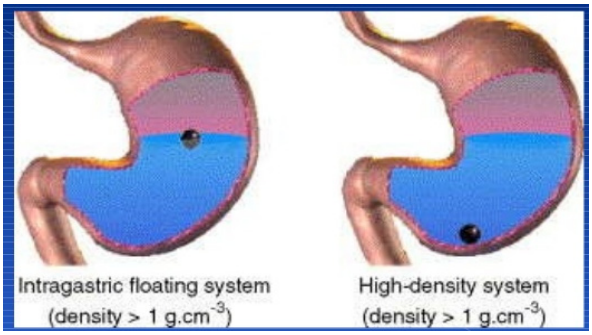
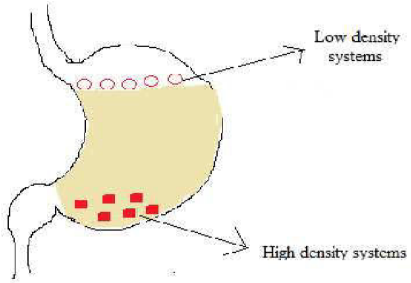


Figure 2(g): High density systems

2.Floating system or Low density system:

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach, (Figure 9), for a prolonged period of time, without affecting the gastric emptying rate and the drug is released slowly

at a desired rate from the system, results in an increase in the gastric residence time and a better control of fluctuations in the plasma drug conentrations and after complete release of the drug, the residual system isemptied from the stomach



(Neha Narang *et al*., 2011).

Figure 2 (h): Low density systems (Floating system)

3.Expandable, unfoldable and swellable systems:

These systems are also called as “Plug type system”, since they exhibit tendency to remain logged in the pyloric sphincters. These polymeric matrices remain in the gastric cavity for several hours even in fed state. By selection of polymer with the proper molecular weight and swelling properties controlled and sustained drug release can be achieved. Upon coming in contact with gastric fluid, the polymer imbibes water and swells.

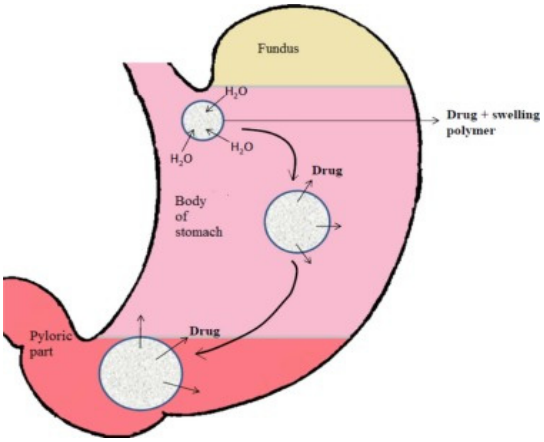


Figure 2(i): Swellable tablet in stomach

(Amit Kumar Nayak *et al*., 2010).

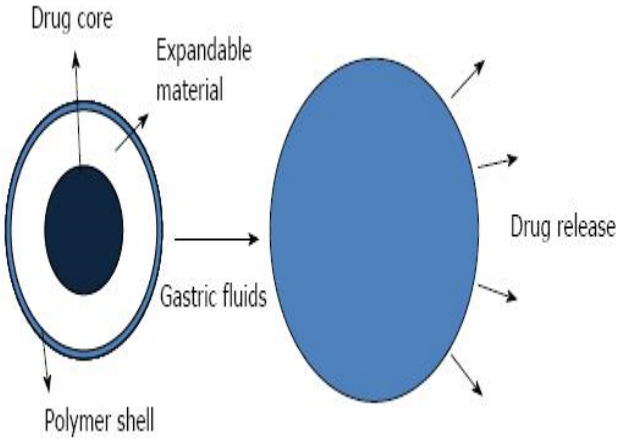


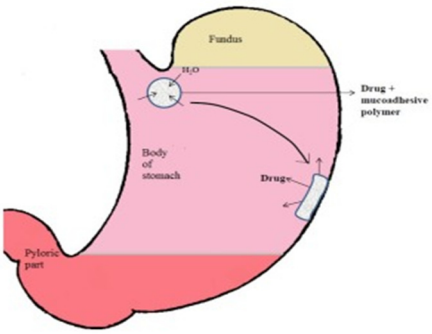
Figure 2(j) : Drug release from swellable systems

Expandable systems have some drawbacks like problematical storage of much easily hydrolysable, biodegradable polymers relatively short-lived mechanical shape memory for the unfolding system most difficult to industrialize and not cost effective. Again, permanent retention of rigid, large single-unit expandable drug delivery dosage forms may cause brief obstruction, intestinal adhesion and gastropathy.

4. Bioadhesive or Mucoadhesive drug delivery systems:

Bioadhesive drug delivery systems are used as materials commonly used for bioadhesion are poly acrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol (PEG) and polylactic acids etc. Even though some of these polymers are effective at producing bioadhesive, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the gastrointestinal tract (GIT).

Figure 2(k) : (Amit Kumar Nayak *et al*., 2010;)



5.Magnetic Systems

This approach to enhance the gastric retention time (GRT) is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

(Anand S. Surana *et al*., 2010; Sunil Kumar *et al.,* 2012).

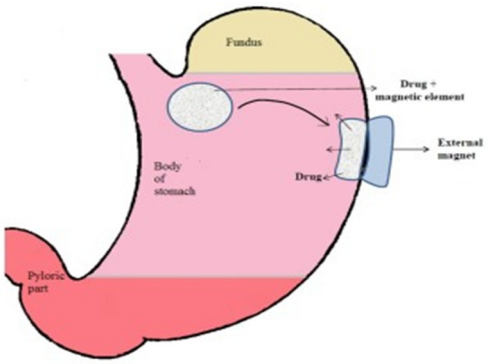


Figure 2(l): Magnetic systems

6. Super porous hydrogel systems: (Harshil P Shah *et al*. 2017)

These swellable systems differ sufficiently from the conventional types to warrant separate classification. In this approach to improve gastric retention time (GRT) super porous hydrogels of average pore size >100 micro meter, swell to equilibrium size within a minute due to rapid water uptake by capillary

wetting through numerous interconnected open pores . They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised by co-formulation of hydrophilic particulate material **(Sunil Kumar *et al*., 2012)**

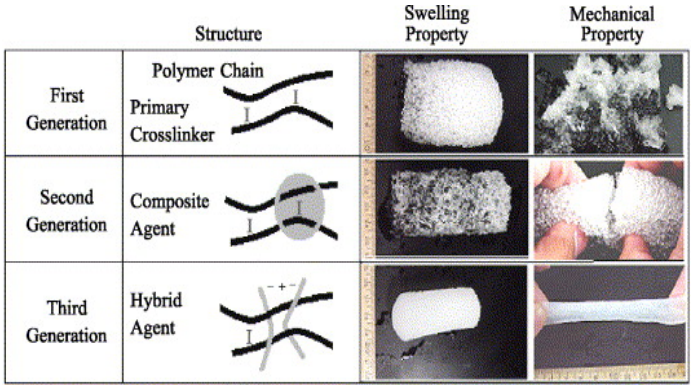


Figure 2 (m): Typical swelling and mechanical properties of the SPH generations.

7. Raft-forming systems:

These systems, contain gel-forming solution (e.g. sodium alginate solution contents, swells and forms a viscous cohesive gel containing entrapped CO_2 bubbles, releases drug slowly in stomach by forming the raft layer on the top of gastric fluid. These formulations contain antacids such as calcium carbonate or aluminium hydroxide to reduce gastric acidity **(Neha Narang *et al*., 2011; Shah S.H *et al*., 2009).**

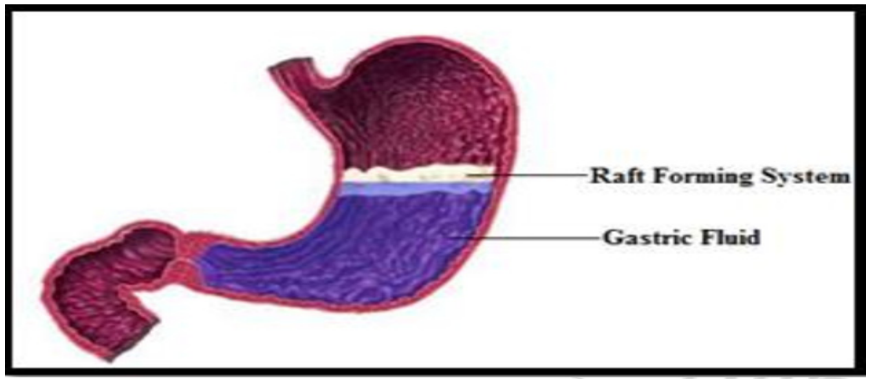


Figure 2(n) : Schematic illustration of the barrier formed by a raft-forming system

CHAPTER 3

FLOATING DRUG DELIVERY SYSTEM- A REVIEW

FLOATING DRUG DELIVERY SYSTEM-REVIEW

The concept of FDDS was first described in the literature as early as 1968, when Davis (1968) disclosed a method to overcome the difficulty experienced by some persons of gagging or choking after swallowing medicinal pills. The author suggested that such difficulty could be overcome by providing pill having a density of less than 1.0g/cm^3, so that pill will float on water surface. Since then several approaches have been used to develop an ideal floating drug delivery system.

MECHANISM OF FLOATING DRUG DELIVERY SYSTEM

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents (Figure 1), the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration **(Praveen Nasa *et al*., 2010).**

However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. The floating force kinetics is measured using a novel apparatus by determining the resultant weight (RW). The RW apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object.

The object floats better if RW is on the higher positive side. This apparatus helpsin optimising FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations **(Shah *et al*., 2009).**

RW or F = F buoyancy - F gravity

= (Df - Ds) gV,

Where,

RW = total vertical force,
Df = fluid density,

Ds = object density,
V = volume and
g = acceleration due to gravity.

In case of gas generating systems, carbon dioxide is released, causing the beads to float in the stomach. And in case of non-effervescent systems, the air trapped by the swollen polymer confers buoyancy to these dosage forms.

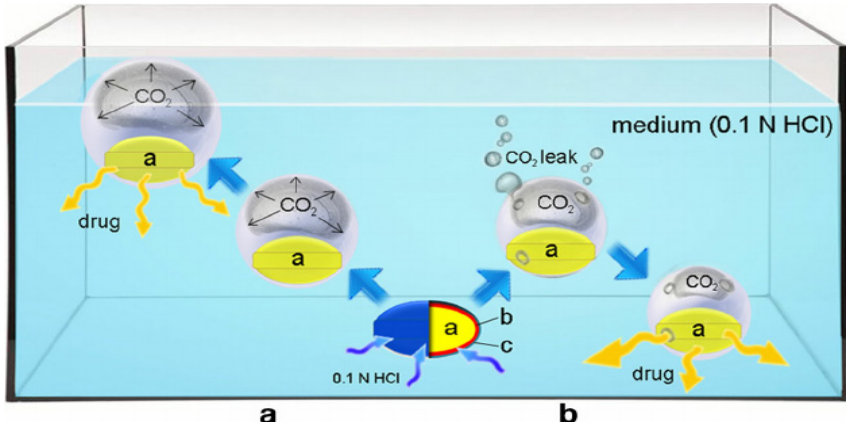


Figure 3(a): Mechanism of Floating systems

CLASSFICATION

Based on the mechanism of buoyancy, two different technologies have been used in development of floating drug delivery systems **(Praveen Nasa *et al*., 2010).** These include:

a) Non- Effervescent system.

b) Effervescent system.

NON-EFFERVESCENT SYSTEM

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in noneffervescent. FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as chitosan and carbopol (Amit Kumar Nayak *et al.,* 2010).

The various types of this system are as

1. Single layer floating tablets.
2. Bilayer floating tablets.
3. Alginate beads.
4. Hollow microspheres.

1.Single layer floating tablets

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity. They are formulated by intimate mixing of drug with low-density enteric materials such as HPMC **(Vinod K.R *et al*., 2010).**

2.Bilayer floating tablets

A bilayer tablet contain **two layer** one immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach **(Vinod K.R *et al*., 2010).**

3.Alginate beads

Multi-unit floating dosage forms were developed from freeze dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causingprecipitation of calcium alginate leading to formation of porous system, whichmaintain a floating force for over 12 hours. hours **(Shah S.H *et al*., 2009; VinodK.R *et al*., 2010).**

4.Hollow microspheres

Hollow microspheres (microballons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method (Figure 3). The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40^0C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in **microsphere of polymer with drug.** The microballons floated continuously over the surface of acidic dissolution media containing surfactant for more **than 12 hours *in vitro* (Vinod K.R *et al*., 2010).**

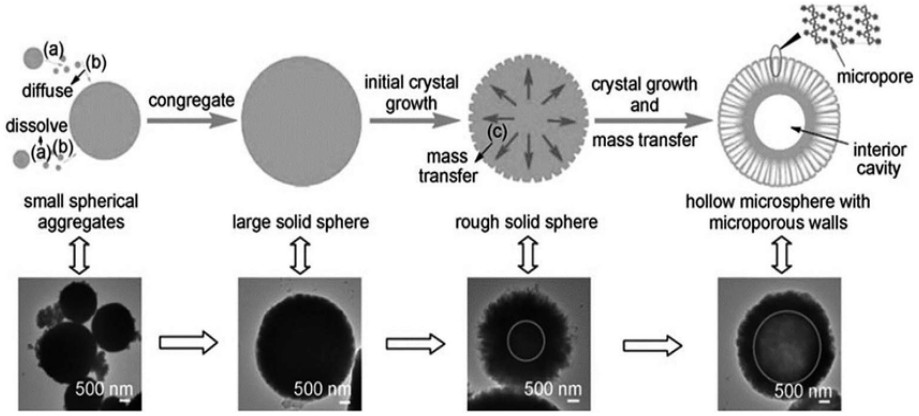


Figure 3(c) : Formulation of floating hollow microsphere or microballoon

EFFERVESCENT SYSTEM

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas. The gas in floating chamber can be introduced either by volatilization of an organic solvent or by effervescent reaction between organic acids and bicarbonate salts **(Shayeda *et al.,* 2009).**

These effervescent systems further classified into two types:

1) Volatile liquid or vacuum containing systems.

2) Gas generating systems.

Volatile liquid or vacuum containing systems

(a) Intragastric floating gastrointestinal drug delivery system

This system floats in the stomach because of floatation chamber, which is vacuum or filled with a harmless gas or air, while the drug reservoir is encapsulated by a microporous compartment **(Vinod K.R *et al.*, 2010).**

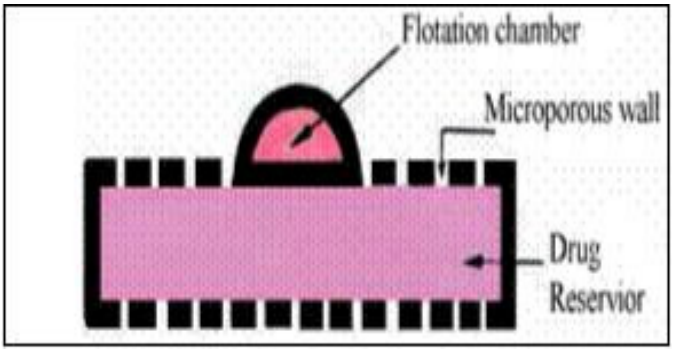


Figure 3(d): Intragastric floating gastrointestinal drug delivery device

b) Inflatable gastrointestinal delivery systems

These systems are incorporated with an inflatable chamber, which contains liquid ether that gasifies at body temperature to inflate the chamber in the stomach. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug is released continuously from the reservoir into gastric fluid **(Vinod K.R *et al*., 2010; Sunil Kumar *et al.,* 2012).**

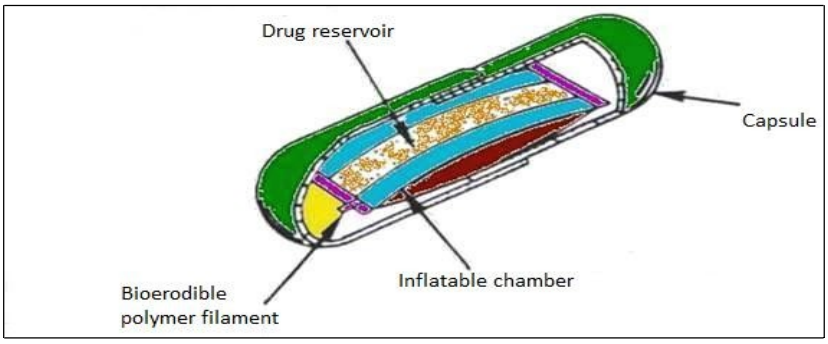


Figure 3(e): Inflatable gastrointestinal delivery system

(c) Intragastric osmotically controlled drug delivery system:

This system is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule, . The inflatable

support inside forms a hollow polymeric bag which contains a liquid that gasifies at body temperature to inflate the bag and it is deformable. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to liquid and vapour and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi-permeable housing. In the stomach, the osmotically active salt present in the osmotically active compartment is dissolved by absorbing the water continuously present in the GI fluid through the semi-permeable membrane. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice. **(Amit Kumar *et al*., 2011; Vinod K.R *et al*., 2010).**

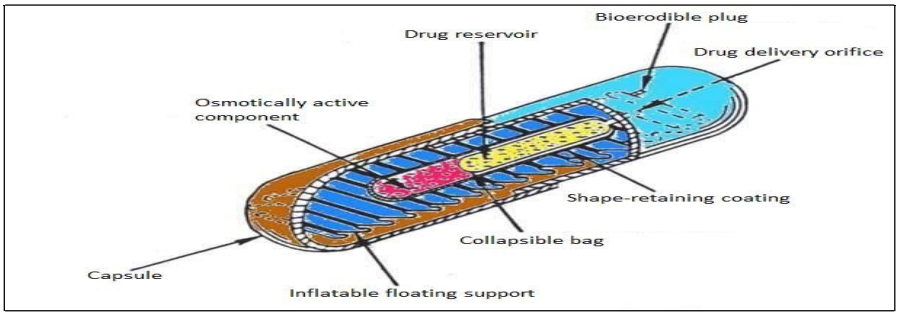


Figure 3(f): Intragastric osmotically controlled drug delivery system

GAS GENERATING SYSTEM

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme **(Sunil Kumar et al., 2012).**

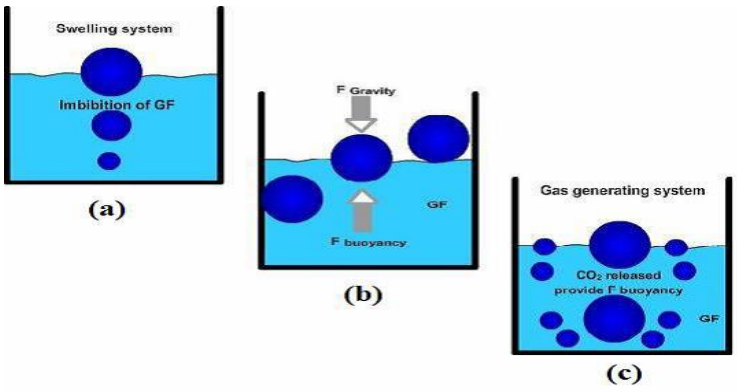


Figure 3(g): Drug release from effervescent (gas generating) systems

A) Tablets:

1. Intragastric single layer floating tablets or Hydrodynamically Balanced System (HBS)

These formulations have bulk density lower than gastric fluids and thus float in the stomach that increases the gastric emptying rate for a prolonged period, (Figure 8). These are formulated by intimately mixing the gas (CO_2) generating agents and the drug within the matrix tablet. The drug is released slowly at a desired rate from the floating system and the residual system is emptied from the stomach after the complete release of the drug. This leads to an increase in the gastric residence time (GRT) and a better control over fluctuations in plasma drug concentration **(**

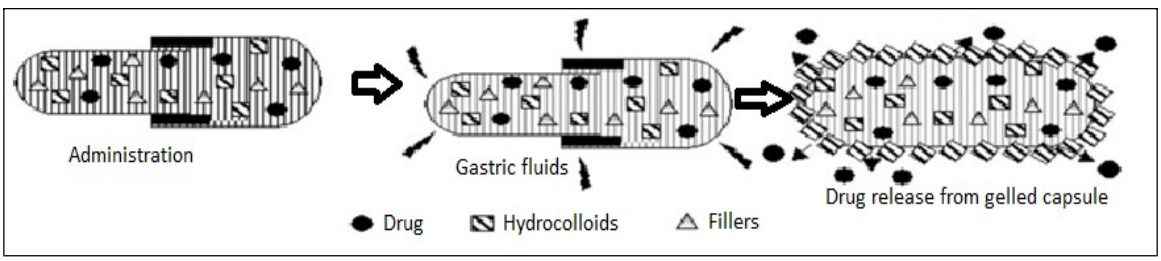


Figure 3(h): Intragastric single layer floating tablet

2. Intragastric bilayer floating tablets

These are also compressed tablets, containing two layers (Figure 9):

- Immediate release layer
- Sustained release layer.

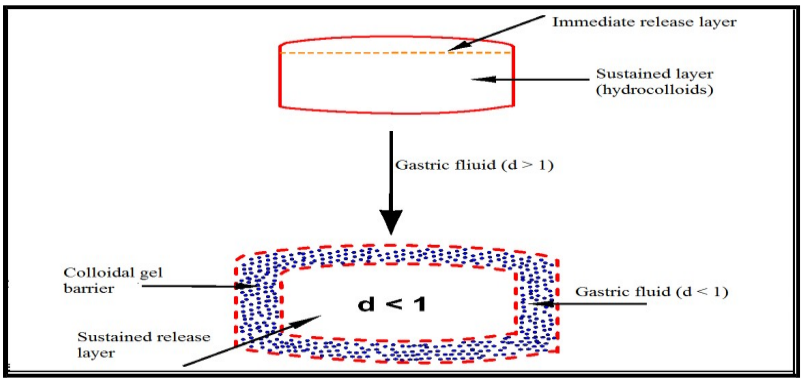


Figure 3(i):Intragastric bilayer floating tablet

B) Floating capsules

These floating capsules are formulated by filling with a mixture of sodium alginate and sodium bicarbonate. The systems float as a result of the generation of CO_2 that was trapped in the hydrating gel network on exposure to an acidic environment **(Vinod K.R *et al*., 2010).**

C) Multiple unit type floating pills

These multiple unit type floating pills are sustained release pills, known as 'seeds', which are surrounded by two layers (Figure 10). The outer layer is of swellable membrane layer while the inner layer consists of effervescent agents. This system sinks at once and then it forms swollen pills like balloons which float as they have lower density, when it is immersed in the dissolution medium at body temperature. The lower density is due to generation and entrapment of CO_2 within the system **(Amit Kumar *et al*., 2011; Vinod K.R *et al*., 2010).**

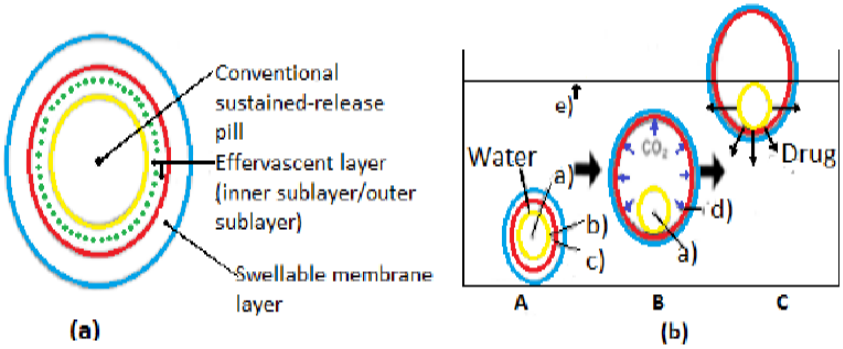


Figure 3(j): Multiple unit type floating pills

D) Floating system with Ion-Exchange resins

Floating system using bicarbonate loaded ion exchange resin was made by mixing the beads with 1M sodium bicarbonate solution, and then the semi-permeable membrane is used to surround the loaded beads to avoid sudden loss of CO_2. On contact with gastric contents an exchange of bicarbonate and chloride ions takes place that results in generation of CO_2 that carries beads towards the top of gastric contents and producing a floating layer of resin beads **(Amit Kumar *et al*., 2011).**

Advantages of Floating drug delivery system (kirti *et al.,* 2013)

1. The FDDS are advantageous for drugs absorbed through the stomach (e.g. ferrous salts) and for drugs meant for local action in the stomach and treatment of peptic ulcer disease (e.g. Antacids).

2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence FDDS may be useful for the administration of aspirin and other similar drugs.

3. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They

dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents.

4. Drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine **(Natasha Sharma *et al*., 2011)**

5. FODDS provides advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region **(Vaishali Sharma *et al.,* 2011)**

Disadvantages of Floating drug delivery system

1. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently coat, water.

2. Drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate **(Natasha Sharma *et al*., 2011)**

3.Drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastro retentive systems **(Vaishali Sharma *et al.,*2011)**

Limitations of gastro retentive drug delivery system:

- The residence time in the stomach depends upon the digestive state. Hence, FDDS should be administered after the meal.
- The ability to float relies on the hydration state of the dosage form. In order to keep these tablets floating *in vivo*, intermittent administration of water (a tumbler full, every 2 h) is beneficial.
- The ability of drug to remain in the stomach depends upon the subject

being positioned upright.

- FDDS are not suitable for the drugs that have solubility or stability problems in the gastric fluid.
- Drugs like nifedipine, which is well absorbed along the entire GIT and which undergoes significant first pass metabolism, may not be desirable candidates for FDDS since the slow gastric emptying may lead to the reduced systemic bio-availability.

EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS

1.PRELIMINARYEVALUATION:

a) Buoyancy Lag Time

It is determined in order to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.

b) Floating Time

Test for buoyancy is usually performed in SGF-Simulated Gastric Fluid maintained at 37^0C. The time for which the dosage form continuously floats on the dissolution media is termed as floating time.

***2)IN VITRO* DISSOLUTION TESTS**

In vitro dissolution test is generally done by using USP apparatus with paddle and GRDDS is placed normally as for other conventional tablets. But sometimes as the vessel is large and paddles are at bottom, there is much lesser paddle force acts on floating dosage form which generally floats on surface. As floating dosage form not rotates may not give proper result and also not reproducible results. Similar problem occur with swellable dosage

form, as they are hydrogel may stick to surface of vessel or paddle and gives irreproducible results. In order to prevent such problems, various types of modification in dissolution assembly made are as follows.

(3) *IN VIVO* EVALUATION (kirti *et al.,* 2013)

a) Radiology

X-ray is widely used for examination of internal body systems. Barium Sulphate is widely used Radio Opaque Marker. So, $BaSO_4$ is incorporated inside dosage form and X-ray images are taken at various intervals to view GR.

b) Scintigraphy

Similar to X-ray, emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used emitting material is 99Tc.

c)Gastroscopy

Gastroscopy is per oral endoscopy used with fibre optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach. It can also give the detailed evaluation of GRDDS.

d)Magnetic Marker Monitoring

In this technique, dosage form is magnetically marked with incorporating iron powder inside, and images can be taken by very sensitive bio-magnetic measurement equipment. Advantage of this method is that it is radiation less and so not hazardous.

e)Ultrasonography

Used sometimes, not used generally because it is not traceable at intestine **(Shweta Arora *et al*., 2005; Gopalakrishnan S *et al.,* 2011).**

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEM

- **Sustained drug delivery: (kirti *et al.,* 2013)**

Hydrodynamically Balanced System (HBS) type are dosage forms which have bulk density less than one, relatively large in size and did not easily pass through pylorus, releases the drug over a prolonged period of time by retaining in the stomach for several hours and by increasing the gastric residence time **(Kwon H. Kim *et al*., 2000).**

- **Site specific drug delivery:**

Floating drug delivery systems are particularly useful for drugs having specific absorption from stomach or proximal part of the small intestine e.g. riboflavin, furosemide etc. The absorption of captopril has been found to be site specific, stomach being the major site followed by duodenum **(Amit Kumar *et al*., 2011).**

- **Absorption enhancement:**

Drugs that have poor bioavailability, because of their absorption is restricted to upper GIT are potential candidates to be formulated as floating drug delivery systems, thereby improving their absolute bioavailability.

- **Minimized adverse activity at the colon**

Retention of the drug at the stomach (HBS system), minimizes the amount of drug that reaches the colon, that prevents the undesirable activities

of the drug in colon. This Pharmacodynamic aspect provides the rationale for GRDF formulation for betalactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

- **Reduction in plasma fluctuations:**

Patients with advanced Parkinson's disease, experienced pronounced fluctuations in symptoms while treatment with standard L-dopa. A HBS dosage form provided a better control of motor fluctuations although its bioavailability was reduced by 50-60% of the standard formulation.

- **Peptic ulcer treatment:**

H. Pylori, causative bacterium for peptic ulcers and chronic gastritis. Patients require high concentration of drug, to be maintained at the site of infection that is within the gastric mucosa. The floating dosage form due to its floating ability was retained in stomach and maintained high concentration of drug in the stomach. A sustained liquid preparation of Ampicillin, using sodium alginate was developed that spreads out and adheres to gastric mucosal surfaces and releases the drug continuously.

- **Suitable for poorly absorbed drugs.**

Floating drug delivery systems are particularly useful for drugs which are poorly soluble or unstable in intestinal fluids and acid stable drugs and for those which undergo abrupt changes in their pH-dependent solubility due to pathophysiological conditions of GIT, food and age, e.g. floating system for furosemide lead to potential treatment of Parkinson's disease. Approximate 30% drug was absorbed after oral administration **(Shweta Arora *et al.*, 2005).**

CHAPTER 4

LITERATURE REVIEW

LITERATURE REVIEW ON FLOATING DRUG DELIVERY SYSTEMS

EFFERVESCENT FORMULATIONS:

Rahim bahiri-najafi *et al* .,2017, developed, floating dosage form containing acyclovir was developed to increase its oral bioavailability. Effervescent floating tablets containing 200 mg acyclovir were prepared by direct compression method with three different rate controlling polymers including Hydroxypropyl methylcellulose K4M, Carbapol 934, and Polyvinylpyrrolidone. Optimized formulation showed good floating properties and *in vitro* drug release characteristics with mean dissolution time and dissolution efficacy of about 4.76 h and 54.33%, respectively. X-ray radiography exhibited that the tablet would reside in the stomach for about 5 ± 0.7 h. After oral administration of floating tablet containing 200 mg acyclovir, the C_{max}, T_{max}, and $AUC_{0-\infty}$ of optimized gastroretentive formulation were found to be 551 ± 141 ng/mL, 2.75 ± 0.25 h and 3761 ± 909.6 ng/mL/h, respectively.

Bharat W Tekade *et al.,* 2017, formulated and evaluated the floating drug delivery system containing Cefpodoxime Proxetil using polymer HPMC K4M, Guar Gum. Effervescent floating tablets containing Cefpodoxime proxetil were prepared by direct compression technique using varying concentrations of different grades of polymer.Physical parameters like hardness, weight variation, thickness and friability were within pharmacopoeial limit. Percentage drug content in all floating tablet formulations was found to be 90% to 110%. The floating time was found to be more than 12 H. floating lag time was found to be 10±2.99 second..% drug release of formulation batch F8 was found to be 96.66% in 0.1 N HCL.

Somnath Bhinge, *et al .,*2017, developed optimized gastric floating drug delivery system (GFDDS) of candesartan celexetil floating tablets by using various

polymers like Eudragit and MCC. In the present work, attempts have been made to prepare candesartan celexetil by direct compression method by using Citric acid, NaHCO3 , Magnesium stearate, Eudragit and MCC. Formulation F4 of sustained release tablet of Candesartan celexetil containing a combination of both polymers was found to be the optimized formulation for 13 hours release as it fulfilled all the requirement of floating drug delivery system of sustained release dosage form.

Adukondalu devendla *et al .*,2017, developed a novel gastro retentive floating tablets of Enalapril Maleate. The main objective is to increase bioavailability and increase gastric residence time. There are 12 formulations were prepared by using different ratios of natural gums & synthetic polymers. Xanthum gum is used for floating property so as to target the delivery of drug to a specific region in the GIT. HPMC K 100 is used as hydrophilic polymer. sodiumbicarbonate, citric acid is used as gas generating agent, Lactose is used as adsorbent, suspending agent. F11was the optimized formulation having floating time more than 20 hrs.

Beena kumari *et al .*,2017, investigated the effect of concentration of HPMC K4M (X), concentration of guar gum (X), concentration of sodium bicarbonate (X) on the release of 1 2 3 atorvastatin calcium using central composite design.The floating tablets were formulated using atorvastatin calcium (20% w/w), HPMC K4M (5-15% w/w), guar gum (5-15% w/w), sodium bicarbonate (4-12% w/w), lactose (q.s.), talc (2% w/w) and magnesium stearate (1% w/w). Atorvastatin calcium floating tablets were evaluated for physical characterization viz. hardness, swelling index, floating capacity, weight variation, friability, in vitro drug release and kinetic studies.

Kharwade RS *et al* ., 2017, evaluated the floating tablets of domperidone that prolongs the gastric residence time using Hibiscus rosa-sinensis mucilage. The directly compressible floating tablets of domperidone were formulated using varying amount of hydroxypropyl methylcellulose K100 M, carbopol 934P and H. rosa-sinensis mucilage. The effervescent components sodium bicarbonate is used for the generation of CO2 gas. Further, tablets were evaluated for in vitro release characteristics. The concentration of H. rosa-sinensis mucilage with a gas-generating agent was optimized to get the sustained release of domperidone. The % cumulative drug release of all formulation from F1 to F6 was within the range of 81.37% to 98.62% for 18 hrs. The release kinetics of all the dosage forms was calculated using zero order, first order, Higuchi, and Korsmeyer–Peppas. It concludes that the release followed zero order release, whereas the correlation coefficient (r2 value) was higher for zero order release.

Hakim singh rajput *et al*., 2017, designed sustained release tablets of Captopril as gastroretentive drug delivery dosage form of a drug meant for management of treat high blood pressure (hypertension), congestive heart failure, kidney problems caused by diabetes, and to improve survival after a heart attack. Formulation of gastroretentive drug delivery dosage forms are done based on optimization under factorial design of formula and classed formulation batches in which concentration of polymer HPMC of various grades (HPMC K15 M, HPMC K100M and HPMC K4M) varied with the ration of sodium bi carbonate and microcrystalline cellulose.

Singh *et al*., 2016, developed a floating matrix tablets of Clarithromycin employing Simplex lattice design. Hydroxypropyl methylcellulose (HPMC) and Ethyl Cellulose (EC) were used as matrix forming agents; Sodium bicarbonate

and citric acid as effervescence producing agents. Total floating time of the formulations was more than 12hours and the drug content was in the range of 98.54±0.46 to 99.92±0.32.

Kanwar N *et al.,* 2016, developed the, Floating tablets of pregabalin were prepare Using different concentrations of the gums (xanthan gum and guar gum), Carbopol 974P NF and HPMC K100. In vitro drug release was higher for tablet batches containing guar and xanthan gum as compared to the batches Containing Carbopol 974P NF. The formulation for a longer period (>12 h).

Ijaz H *et al*., 2015, developed a Gastric floating lisinopril maleate and Metoprolol tartrate bilayer tablets were formulated by direct compression method using the sodium starch glycolate, croscarmellose sodium for IR layer. Eudragit L100,Pectin, acacia as sustained release polymersin different ratios for SR metoprolol tartrate layer and sodium bicarbonate, citric acid as gas generating agents for the floating extended release layer. From the study it is evident that a promising controlled release by floating bilayer tablets of lisinopril maleate and metoprolol tartrate can be developed successfully.

Kadivar A *et al*., 2015, developed an Imatinib mesylate is an antineoplastic agent which has high absorption in the upper part of the gastrointestinal tract (GIT). Floating sustained-release Imatinib mesylate tablets were prepared using the wet granulation method. Tablets were formulated using Hydroxypropylmethylcellulose (HPMC K4M), with Sodium alginate (SA) and Carbomer 934P (CP) as release-retarding polymers, sodium bicarbonate (NaHCO3) as the effervescent agent and lactose as a filler. Formulation to develop 24-hour sustained-release tablets with optimum floating behavior and Satisfactory physicochemical characteristics.

Gao Y *et al*., 2015, developed a gastro-floating sustained-release tablets of troxipide and a further study on in vitro release and in vivo bioavailability. Under the circumstances of direct powder compression, the floating tablets were successfully prepared with HPMC as main matrix material, Carbopol as assistant matrix material, octadecanol as floating agent and sodium bicarbonate as foaming agent to float by gas-forming.

Zhao Q (1) *et al*., 2015, developed a Gastro-floating tablets of ascaridole, a volatile oil were developed to prolong the gastric residence time and thereby, enhance local therapeutic efficacy. The tablets were optimized and prepared by direct compression techniques using Hydroxypropylmethylcellulose (HPMC K15M) and polyethylene oxide (PEO WSRN-750) as Hydrophilic matrices and calcium carbonate (CaCO3) as a gas- generating agent.

Loh ZC *et al*., 2015, developed a Metronidazole which has swelling and floating properties as a gastro retentive controlled-release drug delivery system to improve drug bioavailability. Fifteen different formulations of effervescence-forming floating systems were designed using HPMC K15M, xanthan gum, crospovidone, Eudragit® RL PO,pluronic® F- 127 and/or polypropylene foam powder as swelling agents and sodium bicarbonate with/ without citric acid as gas-forming agents at different compositions. Drug dissolution studies which were carried out using 0.1M HCl at 37°C for 8 hours. Combinations of HPMC K15M and xanthan gum as swelling agents show synergistic effect in retarding drug release and are suitable in providing the most sustained drug release system.

Kesarla RS *et al.,* 2015, developed a Conventional sustained dosage form of Ranitidine hydrochloride (HCl) does not prevent frequent administration due to sIts degradation in colonic media and limited absorption in the upper part of GIT.

FT-IR and DSC indicated no significant incompatibility with selected Excipients. Klucel-LF, POLYOX WSR N 60 K and l-menthol were selected as binder, Polymer and sublimating material, respectively, for factorial design batches after preliminary screening. From the factorial design batches, optimum concentration to release the drug within 12 h was found to be 420 mg of POLYOX and 40 mg of l-menthol. Stability studies indicated the formulation as stable. Ranitidine HCl matrix floating tablets were formulated to release 90%of drug in stomach within 12 h.

Lohithasu D *et al*., 2014. developed the Lafutidine is H2-receptor antagonist. Guar gum is an efficient matrix forming agent in floating tablets by generating gas. Drug release from the prepared tablets was slowed over more 12 h and depended on the composition of guar gum and sodium bicarbonate. Lafutidine release was diffusion controlled and follows zero order kinetics. Floating tablets containing 10 mg of lafutidine could be prepared by wet- granulation technique employing guar gum of different grades as floating polymer and release retardant, methocel K100LVCR, methocel K15M as floating enhancers and sodium bicarbonate as a gas generating agent. Although the tablets with guar gum were able to float for more than 12 h. Resultant tablets blend did not have any incompatibilities showed in FT- IR studies.

El-Zahaby SA *et al*.,2014, developed Gastro retentive levofloxacin (LVF) floating mini-tablets for the eradication of Helicobacter pylori (H. pylori) were prepared using thematrix forming polymer hydroxypropyl methylcellulose (HPMC K100M), alone or with Carbopol 940P indifferent ratios by wet granulation technique. Buoyancy of mini-tablets was achieved by an addition of an effervescent mixture consisting of sodium bicarbonate and anhydrous citric acid to

some formulations. The optimized formula was subjected to further studies: FT-IR, DSC analysis.

Uğurlu T *et al*., 2014, developed to prepare and evaluate clarithromycin (CLA) floating tablets using experimental mixture design for treatment of Helicobacter Pylori provided by prolonged gastric residence time and controlled plasma level.Ten different formulations were generated based on different molecular weight of Hypromellose (HPMC K100, K4M, K15M) by using simplex lattice design (a sub-class of mixture design) with Minitab 16 software. Sodium bicarbonate and anhydrous citric acid were used as gas generating agents. Tablets were prepared by wet granulation technique.

Rao KR *et al*.,2014, the formulated and evaluated Clopidogrel floating tablets were prepared by direct compression technique by the use of three polymers xanthan gum, hydroxyl propyl methylcellulose (HPMC) K15M and HPMC K4M in different concentrations (20%, 25%and 30% w/w). Sodium bicarbonate (15% w/w) and microcrystalline cellulose 30%w/w) were used as gas generating agent and diluent respectively. In-vitro dissolution studies in 0.1 N hydrochloric acid (1.2 pH) The drug release from all the formulations was by non-Fickian diffusion mechanism.

Yin L *et al*., 2013, developed the Gastro-floating tablets of cephalexin were developed to prolong the residence time in major absorption sites. Gastro-floating tablets were prepared and optimized using hydroxypropyl methylcellulose (HPMC K100M) as matrix and sodium bicarbonate as a gas-forming agent. The properties of the tablets in terms of floating lag time, floating time and in vitro release were evaluated. Compared with conventional capsules, the gastro-floating tablets presented a sustained-release behavior with a relative bioavailability of 99.4%,

while the reference sustained-release tablets gave a relative bioavailability of only 39.3%.

Lakshmi P *et al*., 2013, developed the prepare lamotrigine (LM) bilayered and single layered floating tablets and to compare their release profiles. LM floating tablets were prepared by direct compression method. Drug, hydroxyl propyl methyl cellulose K4M, lactose monohydrate and polyvinyl pyrrolidone K30 constitute controlled release layer components and floating layer components includes polymers and sodium bicarbonate..Formulation LFC4 was found to be optimized with dissolution profile of zero order kinetics showing fickian diffusion.

Pawar HA *et al.,* 2013, developed the floating tablets of Atenolol to increase the gastric retention, to extend the drug release, and to improve the bioavailability of the drug. The floating tablets were formulated using hydrophilic polymers as Hydroxy propyl methyl cellulose (HPMC K4M and HPMC K15M), hydrophobic retardant as a hydrogenated cottonseed oil (HCSO), and sodium bicarbonate as a gas generating agent to reduce floating lag time. The in vitro release study of the tablets was performed in 0.1 N HCl as dissolution media. The study also revealed the effectiveness of HCSO as retardant in combination with HPMC.

Gharti K *et al*., 2012, developed the preparation and in vitro evaluation of floating tablets of hydroxypropyl methyl cellulose (HPMC) and polyethylene oxide (PEO) using ranitidine hydrochloride as a model drug. The floating tablets were based on effervescent approach using sodium bicarbonate a gas generating agent. The tablets were prepared by dry granulation method. The effect of polymers concentration and viscosity grades of HPMC on drug release profile was evaluated. The effect of sodium bicarbonate and stearic acid on drug release profile and floating properties were also investigated.

Sathiyaraj S *et al.,* 2011, formulated lornoxicam floating tablets proved that a hydrophobic drug can be designed as modified release dosage form with desired qualities, using hydrophilic polymer HPMC K15M and calcium carbonate as a buoyancy initiator. Additionally, ease of manufacturing process by direct compression implies that it ensures the capability of commer cial utility by large scale production with satisfactory industrial feasibility.

NON-EFFERVESCENT FORMULATIONS:

B.Heeralal *et al.,* 2017, prepared and evaluated non-effervescent drug delivery system of Famotidine HCl ,with different polymers and checked for compatibility using FTIR and DSC. All the formulations were evaluated for differnet parameters like weight variation, drug content and various physic chemical properties.The optimized formulation had controlled formulation upto 12 hrs.Since the value of ncalculated for Korsmeyer-peppas equation was found to be less than 1.0, it indicated that the drug release followed anamolous transport.

C.Haranath *et al.,* 2017, prepared and evaluated Cimetidine non-effervescent floating tablets with Ozokeritewax . Pure drug and optimized formulation FCDO16 were subjected to the drug excipient compatibility studies using FTIR and DSC. The studies revealed that there is no interaction between the drug and excipients. Four formulations were prepared using Ozokerite wax and lactose (FCDO1-FCDO4), it was clearly observed that the drug release was only 16%, 22%, 26% and 32% respectively at the end of 12hr. Therefore in order to increase the drug release different types of superdisintegrants of different categories were chosen along with HPMC K15M as matrixing agent which protects the channels formed by lactose. Superdisintegrants gives the initial startup to the drug release. The super

disintegrants acts as a swelling agent by adsorbing large amounts of aqueous fluids and swells.

Ali Raza *et al.,* 2017, formulatedgastroretentive floating tablets of minocycline hydrochloride with Simplex lattice mixture design to get experimental layout. Methocel K100LV (X1), Methocel K15M (X2) and Carbopol 934 (X3) were selected as independent variables. Ten formulations (F1 to F10) were developed by direct compression and were evaluated for physical parameters, swelling index, floating lag time, floating time and in-vitro drug release rate. Furthermore, FTIR spectroscopic studies were performed to determine drug polymer interaction. Floating lag time (Y1), floating time (Y2), cumulative drug release at 3 h (Y3), 6 h (Y4) and 12 h (Y5) were selected as dependent variables. Results showed that floating lag time and floating time were decreased by presence of Carbopol 934 in formulation while increased by Methocel K100LV and Methocel K15M.. Concisely, concluded that Carbopol 934 and Methocel 100LV can be used to fabricate gastroretentive floating tablets of minocycline hydrochloride with good buoyancy properties and sustained release action.

Amiya kumar prusty *et al* .,2017, developed Gastroretentive floating matrix tablets of the antihyperlipidemic drug Rosuvastatin were successfully prepared using hydrophilic polymers like HPMC K4M and Carbapol. From the Preformulation studies for drug excipients compatibility it was observed that there was no compatibility problem with the excipients used in the study. The Formulated tablets gave satisfactory results for various physicochemical evaluation studies like Weight variation, Floating lag time, Content uniformity, Total floating time, Mucoadhesion time, mucoadhesive strength and in vitro drug release and shows a floating time of around 12 hrs.

Rajendra kumar jadi *et al.,* 2016, developed extended release non-effervescent floating tablets of Propranolol Hydrochloride(PPH) to extend the gastric residence time and prolong the drug release after oral administration.Different viscosity grades of HPMC are used as drug release retardants. Glycerylbehinate and Glycerylmonostearate are used as low density lipids in order to get the desired buoyancy over a prolonged period of time. The drug excipients compatibility was studied using DSC.The prepared tablets wereevaluated for their physical characters, in vitro drug release and in vitro buoyancy.The release and floating property depends on the polymer type, polymer proportion, lipid type and lipid proportions.; The studies revealed a mean gastric residence time of 5 ±1.73 h.

Khalid El-Say *et al.,* 2016, developed optimized non-effervescent floating tablets of Carvedilol by direct compression usinghpmc and carbopol 940 as release retarding polymers.The quality attributes of the tablet are evaluated.The buoyancy lag time , total floating time,swelling ability and in vitro release studies are carried out in 0.1NHCl(ph1.2).Statistical data analysis revealed that the optimized formulation containing 21.91%HPMC and 15% Carbopol940 had acceptable hardness, optimum floating behavior and 24h controlled release pattern.

Swaroopa Arpavalli et al., 2016,developed and evaluatedgastroretentive drug delivery system of fluoroquinolone antibiotics (Balofloxacin). These floating tablets were prepared with the objective to obtain site-specific drug delivery and to extend its duration of action. More over the non effervescent system of balofloxacin will provide increased local and systemic action in stomach. Floating non-effervescent tablets were formulated by various materials like hydroxypropyl methylcellulose HPMC (K 15M, E50), Xanthum gum, Guar gum, Carbopol 976P, polypropylene foam powder were used. All the formulations were evaluated for

floating properties, swelling characteristics and drug release studies. The floating lag time were found to be significantly increased with the increasing concentration of the polymers. After the dissolution study of prepared balofloxacin non-effervescent floating tablet was concluded that the formulation NF9 with HPMC K15 and carbopol 976P show best controlled release effect (98.24%).

Dr.Abdul Hasan Sathali *et al.,* 2016,prepared non effervescentfloating tablets of Tolcaponemethod by using Natural Polymer (Psyllium husk) as floating agent. Psyllium husk is gastric protectant so we can overcome the gastric irritancy caused by the other added chemical excipients. The study included formulation of floating tablets using polymerslikeHydroxy Propyl Methyl Cellulose (HPMC K100, & HPMC K15M), Sodium carboxy methyl Cellulose and Eudragit RS100. The tablets were prepared by direct compression technique. The in-vitro drug release pattern of Tolcapone floating tablets fitted to different kinetic models which showed highest regression for zero order kinetics & all the formulations followed Non-fickian diffusion. Thus the prepared non-effervescent floating tablet of Tolcapone can be used for the treatment of Parkinsonism for more than 12 hrs with single dose administration.

Rakhi Negi *et al.,* 2016., formulated and evaluated microbaloons for Telmisartan which is having poor bioavailability.Telmisartan belongs to class II drug i.e., having high solubility and permeability. The microbaloons for Telmisartan were prepared by using different polymers and ratios.The polymers include ethyl cellulose and HPMC.The obtained microballoons formulations were evaluated for percentage yield, drug content,in-vitro release studies.The optimized formulation was further evaluated.

Meka Vs *et al.,* 2016, formulated non-effervescent floating tablet of Glipizide , a poorly water soluble drug. The solubility of drug initially enhanced using solid dispersion with the help of hydrophobic carriers such as polaxomer,cyclodextrin, and povidone.The optimized formulation was further formulated into non-effervescent floating tablets by using matrix ballooning inducers, such as cross povidone and release retarding agents including HPMC and PEO.All the formulations were within pharmacopoeial limits and all the formulations exhibited good floating behavior.In vitro dissolution studies showed that non-effervescent floating drug delivery systems provide a promising method of achieving prolonged gastric retention time.

Dr. Abdul Hasan Sathali *et al.,* 2015, formulated non-effervescent floating tablets of Valsartan using polymers like HPMC k15M, HPMC k100M, Sodium carboxy methyl cellulose and Eudragit RS100 as a matrix forming agents.Peanut husk powder was used as floating agent.The tablets were prepared by direct compression technique.The in –vitro drug release pattern of valsartan floating tablets fitted into different kinetic models which showed highest regression for zero ordee and koresmeyer-peppas and most of the formulation followed Non-fickian diffusion.

Acharya S *et al*.,2014, developed the study was to optimize HPMC K4M and Carbopol 934 concentration in the development of non-effervescent floating tablets (NEFTs) of glipizide as model drug using 3(2) factorial design. The time required for releasing drug of 50% and 80% and similarity factor were the target responses. HPMC K4M and Carbopol 934 concentrations were the variables. The response surface methodology and optimized polynomial equations were used to select the optimal formulation with desired responses. The excipients used in tablets were

compatible with glipizide as per the results of isothermal stress testing and DSC study. The drug release of entire NEFTs followed zero order kinetics and non-Fickian diffusion mechanism.

Getyala A et *al*., 2013 developed the solubility and bioavailability of Losartan Potassium, by employing non effervescent floating drug delivery (tablet dosage forms). The study included formulation of floating tablets using polymers like Chitosan and Karaya gum as matrix forming agents. Accurel (®) MP1000 was used as floating agent. The tablets were prepared by direct compression technique. FTIR, DSC studies conformed that there was no incompatibility between the polymer and the drug. Tablet showed zero lag time, continuances of buoyancy for >12 h. The tablet showed good in vitro release. Drug release was through swelling and abided by the gellation mechanism. In vivo X-ray studies depicted that tablets continued to float in the GIT for 12 h.

Rajhans S *et al*., 2011, reported that swellable gastro retentive drug delivery system was developed using combination of polyethylene oxide and HPMC K100LV by wet granulation process. based on the release kinetics it can be concluded that this combination of polyox W SR 303 and HPMC K100LV is particularly suitable as gastro retentive drug delivery system of valsartan as extended release drug delivery system.

Yasir M *et al*., 2010, developed one daily SR floating matrix tablet for theophylline using psyllium husk as release controlling polymer and compared the release pattern with synthetic polymer HPMC K100M. It can be concluded that psyllium husk can be a promising polymer for GRFDDS in combination with synthetic polymers (HPMC K15M), and enhanced the floating duration and help to

maintain the dimensional stability at initial stage, which is necessary in case of once daily formulations.

LITERATURE REVIEW ON SOLID DISPERSION

Uddhav Bagul S *et al.,* 2017, prepared and evaluated Glipizide floating tablets.Glipizide belongs to class II drug, hence the solubility must be enhanced. Therefore, the solubility of glipizide was increased by solid dispersion method followed by formulation of floating tablets using 32 full factorial designs. Solid dispersion of PEG 4000 and 6000 with glipizide at dIfferent ratio was prepared by fusion method. The floating tablets were prepared by direct compression method, using HPMC K4M, HPMC K15M and sodium bicarbonate was used to maintain buoyancy. The floating tablets were evaluated for various physiochemical properties and *in vitro* drug release studies. The saturated solubility of pure glipizide was 7.9^g/ml which was enhanced to 204.3^g/ml, after preparation of solid dispersion, in 1:6 ratios with PEG 6000. The glipizide-PEG complex was confirmed by FT-IR spectroscopy and DSC thermo gram.

Gaurav Subash Katore, *et al.,* 2017. Formulated and evaluated controlled release floating tablets of ciprofloxacin with improved solubility & dissolution rate. In present study solid dispersion using various carriers like mannitol & lactose in different ratios were prepared by solvent evaporation method. The prepared solid dispersions were characterized for drug content, solubility & dissolution rate. The dissolution rate substantially improved for ciprofloxacin from its solid dispersions compared with pure drug. Dissolution rate increased with increase in carrier content. The dissolution rate was increased 3 folds with solid dispersions containing 1:4 of drug: lactose. The granules of ciprofloxacin solid dispersion

containing 1:4 of drug: lactose ratio was prepared by wet granulation method using polymer such as ethyl cellulose & HPMC.

Bhujbal Trupti, *et al.,* 2017, developed formulation on nifedipine in the form of bilayer floating sustained release tablet. Bilayer tablet consist of a two layers, immediate release layer and second sustained release layer, compressed in single unit dosage form. Immediate release layer contains surface solid dispersion of nifedipine and floating sustained release layer also contain surface solid dispersion of nifedipine by using HPMC K100M and HPMC K15M as sustained release polymer. Nifedipine is an antihypertensive drug. Surface solid dispersion of nifedipine was prepared by solvent evaporation method with different super disintegrant as a polymer for improvement of solubility resulting in improved bioavailability. Immediate release layer releases the drug immediately and floating sustained release layer floats on gastric fluid for upto 12 hours and releases the drug in sustained manner, subsequently it prolongs duration of action.

Al Zahra Al Ashmway *et al.,* 2016, prepared and evaluated floating tablets of Atorvastatin Calcium . Physical mixtures of ATC were prepared by mixing the appropriate amounts of ATC and carriers (PVP k-2000, PEG 6000 and skimmed milk) in geometric proportions using a mortar and pestle, until a homogeneous mixture was obtained. Solid dispersions of ATC with all carriers were prepared at ratios of (1:1, 1:3, 1:5, 1:7 and 1:9 drug to carrier ratio w/w) by three methods, kneading method, solvent evaporation and melting method. Evaluation of solid dispersion was done by studying the phase solubility, *in-vitro* dissolution, FTIR spectroscopy, DSC and X-ray powder diffractometry. The selected solid dispersion formulation was incorporated in floating tablets which were prepared by melting

granulation method. PEG 6000, PVP k-2000 and skimmed milk increased the solubility of ATC by 180, 290 and 1200 folds, respectively.

Yang Zhao*. et al .,* 2014, prepared enteric solid dispersion (SD) for Nimodipine delayed release tablets via melting method. The physical state of the dispersed NMD in the polymer matrix was characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and dissolution studies. Compared with pure drug and physical mixture, the dissolution of NMD-SD was enhanced dramatically (about 80%). As shown in the dissolution studies, the tablet released less than 10% in the artificial gastric acid in the initial 2 h and released 32.1%, 75%, more than 90% at 4, 10 and 14 h respectively in the artificial intestinal fluid. This investigation has solved the problems of oral solid dosage forms of NMD, and it has the good industry prospect.

LITERATURE REVIEW ON FEBUXOSTAT

Ketan Savjini *et al.,* 2015, had developed a modified release formulation of febuxostat that can serve the dual purpose of increasing the efficacy and decreasing the toxicity, thereby improving safety. Pharmacokinetic and pharmacodynamic data, including drug concentration profile, efficacy data and toxicity data have been reviewed thoroughly. Based on available data, target pharmacokinetic profile had been identified as about 50 % reduction in C max. The developed formulation was a potential candidate for filing to a regulatory agency with the advantage of higher efficacy and less toxicity, which will be beneficial to the patient population and has good commercial viability.

Mukesh Sharma *et al.,* 2014, prepared swellable gastro retentive floating tablet by direct compression technique and evaluated for their swelling characteristics (Swelling index, water uptake), floating capacity (floating lag time

and duration), Invitro drug release and stability studies. Factorial design was employed to optimize formulation components. The floating lag time and time required for 90% (t90%) of drug release were selected as dependent variables. Polymer with lower viscosity (HPMC K4M) was shown to be beneficial than higher viscosity polymer (K15M and K100M) in improving the floating properties of GRDDS.

Prashanth Bhide *et al.,* 2012, developed sublingual formulation by direct compression method, where superdisintegrants like crospovidone, Kyron T-114®, sodium starch glycolate, croscarmellose sodium, Tulsion 339® and Indion 234® were used to enhance solubility and drug release rate. The tablets were evaluated for hardness, thickness, friability, weight variation, drug content, wetting time, in-vitro disintegration time, water absorption ratio and in-vitro dissolution studies. It was concluded that sublingual tablet containing Kyron T-114® and crospovidone showed the highest release (95.37%) at the end of 8 minutes.

CHAPTER 5

AIM OF WORK

AIM OF WORK

A conventional dosage forms can only partly satisfy the therapeutic and biopharmaceutical needs, as it doesn't take into account the site specific absorption rates within the GIT, therefore there is a need for developing delivery system that release the drug at the right time, at the specific site and with the desired rate.

To overcome these problems, different approaches have been proposed to retain dosage form in the stomach. One of the most feasible approach for achieving a prolonged and predictable drug delivery in the GIT is to control the Gastric Residence Time (GRT) (i.e. Gastro retentive dosage form). This dosage form can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GIT, thus ensuring optimal bioavailability. Gastro retention can be achieved via Intragastric floating drug delivery system, High density system, Swelling (or) Expandable system and Superporous hydrogels.

The purpose of the present work was to develop an optimized floating drug delivery system for the treatment of gout using xanthine oxidase inhibitor Febuxostat.

Febuxostat is insoluble in water, solubility of Febuxostat enhanced by solid dispersion using PEG 6000 as a hydrophilic carrier by melting technique. Hydrophilic carrier forms hydrophilic bond with the drug which controls release of drug, improving solubility in acidic environment, and reduces the initial burst effect due to gas generating agent.

Gout is the collective name for several disorders that are characterized by the formation and deposition of monosodium urate (MSUr) crystals. The condition is associated with recurrent episodes of acute joint pain due to the deposition of MSUr crystals in the synovial fluid. The half life of Febuxostat is about 3 to 5 h. Therefore to avoid the repetitive administration of Febuxostat and to reduce total dose the gastroretentive drug delivery of Febuxostat is developed.

SOLID DISPERSIONS (Patel B P *et al.*, 2012).

One of the main drawbacks of effervescent floating formulation is the extent of initial burst effect due to excess carbon dioxide generation. Reducing the proportion of effervescent compounds could solve the problem.

An alternative way to restrain burst effect is by the use of solid dispersions as drug carriers, a technique that is proven to be efficient without the need to reduce the proportion of the effervescent agents in the formulation.

The term **'solid dispersions'** refers to a family of multi-component systems where by a crystalline or amorphous drug is dispersed into an amorphous or semicrystalline polymer matrix. The release rate of the resultant formulations is greatly affected by the physical state of the dispersed drug, which in turn is defined by the solubility of the drug in the polymer.

Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution, absorption and therapeutic efficacy of drugs in dosage forms. The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting- solvent method.

There are many methods available for enhancing solubility through solid dispersion. Here , I have employed **MELTING METHOD.**

In Melting method, drug (FEBUXOSTAT) and carrier(PEG6000) are mixed using mortar and pestle. To accomplish a homogenous dispersion the mixture is heated at or above the melting point of all the components. It is then cooled to acquire a congealed mass. It is crushed and sieved**. (Kalaiselvan et al., 2006)**

COMPARISION BETWEEN EFFERVESCENT TECHNIQUES AND NON-EFFERVESCENT TECHNIQUES

Effervescent floating drug delivery systems are the promising techniques in gastro retentive drug delivery systems. Effervescence leads to increase in rate and extent of absorbtion of drugs that are known to have poor bioavailability, by

- Reducing thickness/viscosity of the mucus layer present adjacent to GI mucosa.
- Alteration of tight junctions b/w cells, promoting absorption through paracellular route.
- Increasing hydrophilic environment within cellular membrane.
- The effectiveness of this type of system can be reduced by fluctuation in gastric ph due to factors like disease condition and presence of food.

Hence, it is better to have an alternating technique called

NON-EFFERVESCENT technique, which employs a mechanism of swelling after swallowing through imbibitions of gastric fluid to an extent that it prevents their exit from the stomach.

In patients who is denied having sodium intake in diseased conditions, this technique is more effective.

Thus , this study is to compare both the effervescent and non-effervescent formulations having similar excipients (Hydrophobic and hydrophillic) and determining their properties with respect to each other.

CHAPTER 6

PLAN OF WORK

PLAN OF WORK

1. STANDARD CALIBRATION CURVES FOR FEBUXOSTAT:

a) Preparation of dissolution medium Acid buffer pH1.2

b) Determination of (Absorbance maximum) λ max of Febuxostat by UV Spectrum.

c) Preparation of standard calibration curve for Febuxostat.

2. DRUG - POLYMER COMPATIBILITY STUDIES:

a) Fourier transform Infrared spectroscopic (FTIR) studies.

b) Differential scanning calorimetric (DSC) studies.

3. FORMULATION AND EVALUATION OF FEBUXOSTAT GASTRO RETENTIVE FLOATING TABLETS.

a) Formulation of solid dispersion complexes.

b) Estimation of percentage yield and drug content

c) Formulation of Febuxostat floating matrix tablets by both Effervescent and Non-Effervescent techniques.

d) *Invitro* dissolution studies

e) Comparision between effervescent drug release and non- effervescent drug release patterns.

f) Selection of best formulation.

4.EVALUATION OF FEBUXOSTAT GASTRO RETENTIVE FLOATING TABLETS:

a) Pre compressional evaluation of powder blend:

- Angle of repose
- Bulk density
- Tapped density
- Compressibility index
- Hausner's ratio
- Drug content

b) Post compressional evaluation of floating tablets:

- General appearance
- Tablet dimension
- Hardness
- Friability
- Weight variation
- Drug content
- *Invitro* buoyancy studies
- Swelling studies
- *Invitro* release studies
- *Invitro* drug release kinetics studies.
- Selection of best method and formulation.
- Evaluation of best formulation
  - Fourier transform Infrared spectroscopic (FTIR) studies.
  - Differential scanning calorimetric (DSC) studies.
  - Powder X-Ray diffraction (PXRD) studies.
  - In- vivo X- ray studies.

CHAPTER 7

MATERIALS AND EQUIPMENTS

MATERIALS

S.No	Name of material	Manufacturer / supplier	Use in formulation
1	FEBUXOSTAT	Pure Chem Pvt Ltd.	Active ingredient
2	HPMC K100	Madras Pharma, Chennai.	Hydrophilic polymer
3	HPMC K4	Madras Pharma, Chennai.	Hydrophilic polymer
4	PVPK30	Madras Pharma, Chennai.	Binding agent
5	Sodium bicorbonate	Fourrts India Laboratories Pvt Ltd	Effervescent Agent
6	Citric Acid	Fourrts India Laboratories Pvt Ltd.	Effervescent Agent
7	Micro crystalline cellulose	Paris Dakner Pvt Ltd.	Binding agent
8	Methyl cellulose	Paris Dakner Pvt Ltd.	Hydrocolloid
9	Ethyl cellulose	Paris Dakner Pvt Ltd.	Buoyancy increasing agent.
10	Talc	Paris Dakner Pvt Ltd	Glidant
11	Magnesium stearate	Paris Dakner Pvt Ltd	Glidant

EQUIPMENTS

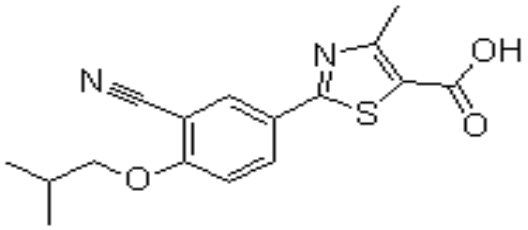
S.No	EQUIPMENT'S / INSTRUMENTS	MANUFACTURER / SUPPLIER
1	Electronic weighing balance	A & D company HR 200, Japan.
2	Hot air oven	RANDS Instruments Company, Chennai.
3	Multi Punch tablet compression machine	Fluid pack Co.Pvt., Ahmadabad
4	Vernier caliper	Linker, Mumbai.
5	Monsanto hardness tester	Praveen Enterprises, Bangalore.
6	Friability Test Apparatus	Indian Equipment Corporation.
7	pH meter	MC Dalal, Chennai
8	Disintegration apparatus	Electrolab, India
9	Digital Tablet Dissolution Test Apparatus	Disso 2000 Lab India, Mumbai.
10	UV-visible spectrophotometer	UV-1700 Pharmaspec Shimadzu, Japan
11	Fourier transform infra-red spectrophotometer	Shimadzu RXI Japan.

CHAPTER 8

DRUG PROFILE

DRUG DATA:

Febuxostat:



Structure:

IUPAC name: 2-[3-Cyano-4-isobutoxyphenyl]-4-methylthiazole-5-carboxylic acid; 2- [3-Cyano-4-(2-methylpropoxy) phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid.

Molecular Formula: $C_{16}H_{16}N_2O_3S$.

Molecular Weight: 316.37.

CAS Registry Number: 144060-53-7

Solubility: Febuxostat is practically insoluble in water, soluble in methanol, soluble in DMSO, sparingly soluble in acetone.

Half life: Mean elimination half-life of approximately 4 to 6 hours.

Description: Febuxostat is in the crystalline form having off white powder to pale yellow in colour.

Dose: Suggested dose: 40-120 mg daily (40mg, 80 mg two times a day).

Excretion: Febuxostat is eliminated by renal pathway.

Storage: Store at controlled room temperature 20°C-25°C.

Melting point: 238°C to 239 °C.

Pharmacokinetics data:

Absorption : >49%

Protein binding : 99.2%

Half-life : 5-8 hrs

pH range : 1-5

pka Value : 3.08

Identification : 317 nm in UV spectrophotometer

Route of administration : oral

Dose : 40mg, 80mg, 120mg

Dosage form : tablets

Therapeutic categories : xanthine oxidase inhibitor

USE

For the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis). It is indicated for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS). Febuxostat has therapeutic index in the gout disease and so pharmacokinetically is safe since normal doses can vary from 40 to 120 mg per day with no substantial difference in acute toxicity or effect.

Volume of distribution :0.7L/kg.

Time to reach peak plasma concentration:5hr

Urinary excretion: Approximately 45%

No dose adjustment is necessary when administering febuxostat in patients with mild to moderate renal and hepatic impairment.

Metabolism:

Febuxostat is extensively metabolized by both conjugation via uridine diphosphate glucuronosyltransferase (UGT) enzymes including UGT1A1, UGT1A3, UGT1A9, and UGT2B7 and oxidation via cytochrome P450 (CYP) enzymes including CYP1A2, 2C8 and 2C9 and non-P450 enzymes. The relative contribution of each enzyme isoform in the metabolism of febuxostat is not clear. The oxidation of the isobutyl side chain leads to the formation of four pharmacologically active hydroxy metabolites, all of which occur in plasma of humans at a much lower extent than febuxostat. In urine and feces, acyl glucuronide metabolites of febuxostat (~35% of the dose), and oxidative metabolites, 67M-1 (~10% of the dose), 67M-2 (~11% of the dose), and 67M-4, a secondary metabolite from 67M-1 (~14% of the dose), appeared to be the major metabolites of febuxostat in vivo.

PHARMACODYNAMIC MECHANISM OF ACTION:

Febuxostat is a non-purine selective inhibitor of xanthine oxidase. It works by non-competitively blocking the molybdenum pterin center which is the active site on xanthine oxidase. Xanthine oxidase is needed to successively oxidize both hypoxanthine and xanthine to uric acid. Hence, febuxostat inhibits xanthine oxidase, therefore reducing production of uric acid. Febuxostat inhibits both, oxidized as well as reduced form of xanthine oxidase because of which febuxostat cannot be easily displaced from the molybdenum pterin site.

Clinical efficacy:

Many long and short-term clinical trials have proved the efficacy of Febuxostat in the treatment of gout and lowering uric acid levels. Febuxostat was found to be superior to Allopurinol in reducing the serum uric acid levels.

Febuxostat versus Allopurinol Controlled Trial (FACT): Serum urate levels were reduced below 6.0 mg/dL at the last three monthly observations in a significantly greater proportion of patients with gout and hyperuricemia receiving febuxostat 80 or 120 mg once daily than in those receiving allopurinol 300 mg once daily in a 52-week, randomized, double-blind trial.

Allopurinol Placebo controlled Efficacy study of febuXostat (APEX): Febuxostat 80, 120 or 240 mg once daily showed significantly greater urate-lowering efficacy than allopurinol 100 or 300 mg once daily in a 28-week, randomized, double-blind, placebo- controlled trial in patients with gout and hyperuricemia**.(GOUT UPDATE BPJ ISSUE 62).**

Side effects:

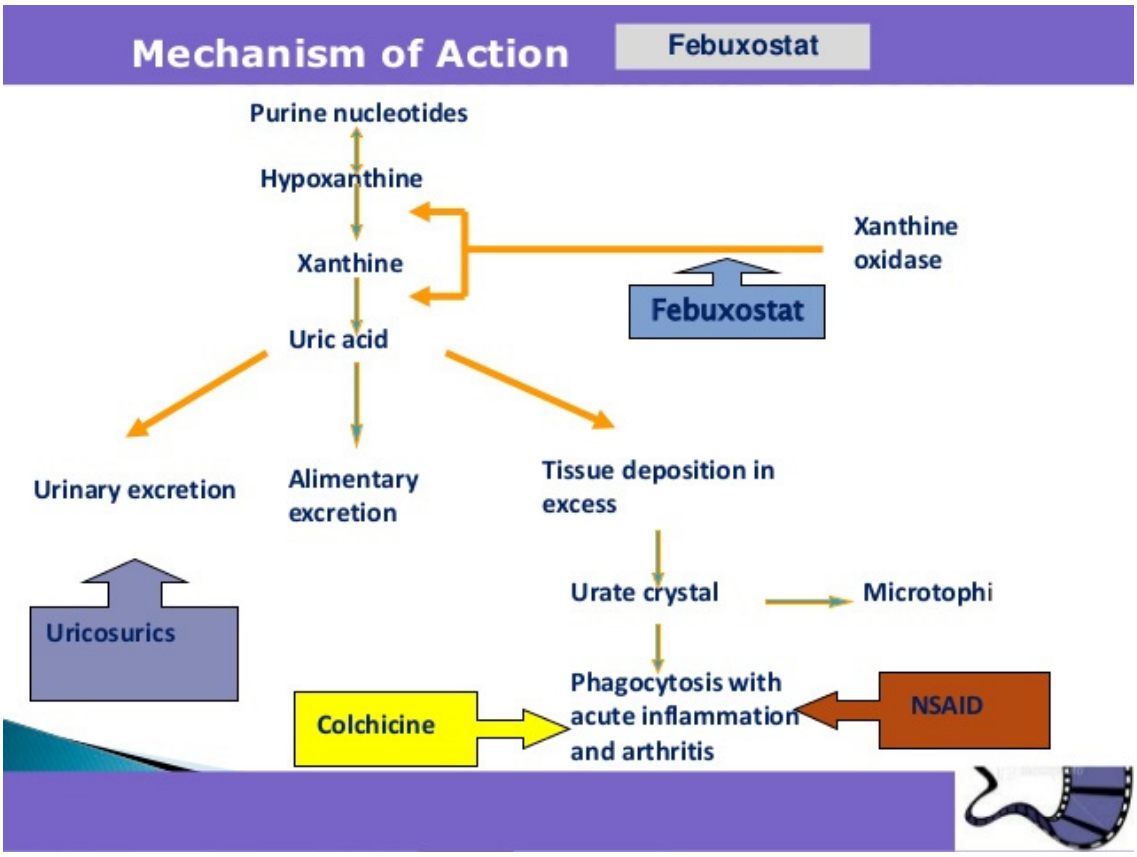
The adverse effects associated with febuxostat therapy include nausea, diarrhea, arthralgia, headache, increased hepatic serum enzyme levels and rash.

Drug interaction:

Drugs metabolized by xanthine oxidase (eg, azathioprine, mercaptopurine, theophylline). Plasma concentrations of these agents may be increased, leading to toxicity. Coadministration with febuxostat is contraindicated.

Toxicity :

Liver test abnormalities have been reported to occur in 2% to 13% (average ~3.5%) of patients receiving febuxostat, but the levels are generally mild-to-moderate and self-limited. The height, nature and timing of these abnormalities have not been described. However, liver test elevations were the major reason for febuxostat discontinuation for adverse events (~2%) in clinical trials, despite the fact that no cases of jaundice or acute hepatitis were reported. The product labeling for febuxostat, however, lists potential side effects of hepatic steatosis, hepatitis and hepatomegaly. Another unrelated, nonpurine xanthine oxidase inhibitor (benzbromarone) was not approved for use in the United States because of its potential for hepatic toxicity.

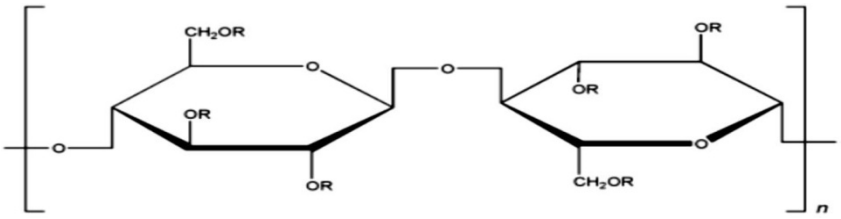


CHAPTER 9

EXCIPIENTS PROFILE

HYDROXYPROPYL METHYL CELLULOSE :

Structural Formula:



Where, R is H, CH3, or CH3 CH (OH) CH2

Non-proprietory Names:

BP: Hypromellose
USP: Hydroxypropyl methyl cellulose 2208, 2906, 2910

Synonyms:

Methyl hydroxypropyl cellulose, Methocel, Methyl cellulose

Chemical Name and CAS Registry Number:

Cellulose Hydroxypropylmethyl ether [9004–65–3]

Solubility:

Soluble in cold water, forming a viscous colloidal solution, practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol & dichloro methane.

PH:

5.5–8.0 for a 1% w/w aqueous solution.

Melting point:

Browns at 190–200°C, chars at 225–230°C. Glass transition temperature is 170–180°C.

Density:

1.326 g/ cm3

Molecular weight:

Approximately 10,000 to 15,00,000

Functional Category:

Bioadhesive material; coating agent; controlled-release agent; dispersing agent; dissolution enhancer; emulsifying agent; emulsion stabilizer; extended-release agent; film-forming agent; foaming agent; granulation aid; modified-release agent; mucoadhesive; release-modifying agent; solubilizing agent; stabilizing agent; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity- increasing agent.

Applications in Pharmaceutical Formulation:

- Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations.
- In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes.
- High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%.
- ypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undissolved fibers present, and is therefore preferred in formulations for ophthalmic use.

Description:

An odorless and tasteless, white or creamy-white fibrous or granular powder.

Solubility:

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%) and ether.

Acidity/alkalinity:

pH = 5.0–8.0 for a 2% w/w aqueous solution.

Stability and Storage Conditions:

Very stable in dry conditions. Solutions are stable at pH 3.0 – 11.0. Stored in a well closed container, in a cool, dry place.

Incompatibilities:

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hypromellose dust may be irritating to the eyes, so eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible.

Regulatory Status:

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (ophthalmic and nasal preparations; oral capsules, suspensions, syrups, and tablets; topical and vaginal preparations).

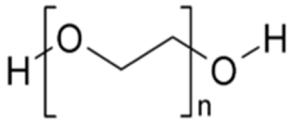
POLYETHYLENE GLYCOL 6000

Polyethylene glycol 6000 (PEG) is a polyether compound with many applications from industrial manufacturing to medicine. The structure of PEG is (note the repeated element in parentheses):

$HO\text{-}CH_2\text{-}(CH_2\text{-}O\text{-}CH_2\text{-})_n\text{-}CH_2\text{-}OH$

PEG is also known as polyethylene oxide (PEO) or polyoxyethylene (POE), depending on its molecular weight.

Polyethylene glycol, referred to as PEG, is used as an inactive ingredient in the pharmaceutical industry as a solvent, plasticizer, surfactant, ointments and suppository base, and tablet and capsule



lubricant. PEG has low toxicity with systemic absorption less than 0.5%.

Structure

Nonproprietary Names: Carbowax, GoLYTELY
GlycoLax, Fortrans
TriLyte, Colyte

Boiling Pt: Min. 250°C (101hPa)

Melting Pt: 55 to 62 °C

Density: 1.13 g/cm³ (20°C)

Appearance White or almost white, waxy or paraffin-like

Solubility: Soluble in water

Synonyms

PEG; Macrogol; Polyoxyethlene; Aquaffin; Nycoline alpha-hydro-omega-hydroxypoly(oxy- 1,2-ethanediyl); polyethylene glycols; Poly Ethylene Oxide; Polyoxyethylene;

Empirical Formula and Mol. Weight

H(OCH2CH2)nOH [average 6000 g/mol]

Functional Category

Lubricating agent , solubilizing agent, coating agent

Applications in Pharmaceutical Formulation or Technology

Chemical uses

- Polyethylene glycol has a low toxicity and is used in a variety of products.[16] The polymer is used as a lubricating coating for various surfaces in aqueous and non-aqueous environments.
- Since PEG is a flexible, water-soluble polymer, it can be used to create very high osmotic pressures (on the order of tens of atmospheres). It also is unlikely to have specific interactions with biological chemicals. These properties make PEG one of the most useful molecules for applying

osmotic pressure in biochemistry,and biomembranesexperiments, in particular when using the osmotic stress technique.

- Polyethylene glycol is also commonly used as a polar stationary phase for gas chromatography, as well as a heat transfer fluid in electronic testers.
- PEG is often used (as an internal calibration compound) in mass spectrometry experiments, with its characteristic fragmentation pattern allowing accurate and reproducible tuning.
- PEG derivatives, such as narrow range ethoxylates, are used as surfactants.
- PEG has been used as the hydrophilic block of amphiphilic block copolymers used to create some polymersomes.

SODIUM BICARBONATE

Functional Category:

USP: Alkalizing agent
BP: Antacid; systemic alkalinizing substance

Synonyms:

Sodium hydrogen carbonate, sodium acid carbonate, baking soda

Chemical Name and CAS Registry Number:

Carbonic acid monosodium salt [144-55-8]

Empirical Formula: $NaHCO_3$

Molecular weight: 84.01

Applications in Pharmaceutical Formulation:

- Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation.
- Tablets may also be prepared with sodium bicarbonate alone since the acid of gastric fluid is sufficient to cause effervescence and disintegration. Sodium bicarbonate is also used in tablet formulations to buffer drug molecules that are weak acids, thereby increasing the rate of tablet dissolution and reducing gastric irritation.
- Additionally, sodium bicarbonate is used in solutions as a buffering agent for erythromycin, lidocaine, local anesthetic solutions, and total parenteral nutrition (TPN) solutions. In some parenteral formulations, e.g. niacin, sodium bicarbonate is used to produce a sodium salt of the active ingredient that has enhanced solubility Sodium bicarbonate has also been used as a freeze-drying stabilizer and in toothpastes.

Table 5: Uses of sodium bicarbonate

Use	Concentration (%)
Buffer in tablets	10-40
Effervescent tablets	25-50
Isotonic injection/infusion	1.39

Description:

An odorless, white crystalline powder with a slightly alkaline taste. The crystal structure is monoclinic prisms. Grades with different particle sizes, from a fine powder to free-flowing uniform granules, are commercially available.

Acidity/alkalinity:

pH = 8.3 for a freshly prepared 0.1Maqueous solution at 258C; alkalinity increases on standing, agitation, or heating.

Solubility:

Water: 1 part in 11 parts (20^{O}C), 1 part in 4 parts (100^{O}C), Ethanol (95%; 20^{O}C): insoluble; Ether (20^{O}C): practically insoluble.

Melting point:

270^{O}C with decomposition.

Hygroscopicity:

At relative humidities below 80%, the moisture content is less than 1%. Above 85% relative humidity, it rapidly absorbs excessive amounts of water and may start to decompose.

Stability and Storage Conditions:

Upon heating at 250^{O}C to 300^{O}C, sodium bicarbonate decomposes and is converted into anhydrous sodium carbonate. Sodium bicarbonate is stable in dry air but slowly decomposes in moist air and should therefore be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Sodium bicarbonate reacts with acids, acidic salts and many alkaloidal salts, with the evolution of carbon dioxide. It can also intensify the darkening of salicylates. In powder mixtures, atmospheric moisture or water of crystallization from another ingredient is sufficient for sodium bicarbonate to react with compounds such as boric acid or alum.

Handling Precautions:

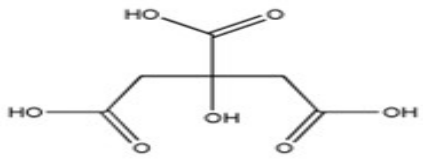
Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

Regulatory Status:

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (injections; ophthalmic preparations; oral capsules, solutions, and tablets).

CITRIC ACID

Structural Formula:



Synonyms:

2-hydroxypropane-1, 2, 3-tricarboxylic acid monohydrate

Empirical Formula:

C6H8O7•H2O

Molecular weight:

210.14 g/mol

Functional Category:

Acidifying agent, antioxidant, buffering agent, chelating agent, flavor enhancer.

Description:

Citric acid monohydrate occurs as colorless or translucent crystals, or as a white crystalline, efflorescent powder. It is odorless and has a strong acidic taste.

Solubility:

Soluble 1 in 1.5 parts of ethanol (95%) and 1 in less than 1 part of water; Sparingly soluble in ether.

pH :

2.2 (1% w/v aqueous solution

Melting point:

≈100°C (softens at 75°C)

Density:

1.542 g/cm3

Incompatibilities:

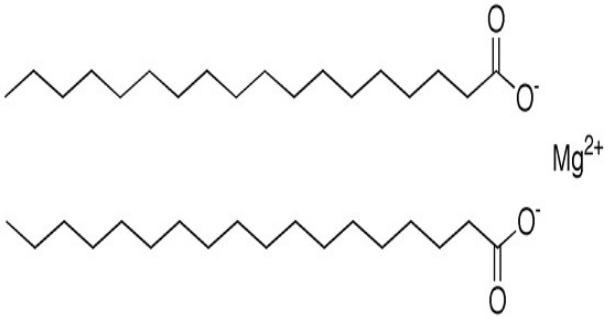
Citric acid is incompatible with potassium tartrate, alkali and alkaline earth carbonates and bicarbonates, acetates, and sulfides. Incompatibilities also includeoxidizing agents, bases, reducing agents, and nitrates.

Applications:

- Citric acid monohydrate is used in the preparation of effervescent granules, while anhydrous citric acid is widely used in the preparation of effervescent tablets.
- Citric acid has also been shown to improve the stability of spray-dried insulin powder in inhalation formulations.
- In food products, citric acid is used as a flavor enhancer for its tart, acidic taste.
- Citric acid monohydrate is used as a sequestering agent and antioxidant synergist.

(Hand book of Pharmaceutical Excipients by Raymond C. Rowe et.al., 2009)

MAGNESIUM STEARATE



Structure:

Structural Formula:

[CH3 (CH2)16COO] 2Mgs

Synonyms:

Dibasic magnesium stearate; Magnesium distearate; Magnesiistearas; Magnesium octadecanoate; Octadecanoic acid,

magnesium salt; Stearic acid; Magnesium salt; Synpro90.

Empirical formula:

C36H70MgO4

Molecular weight:

591.24 g/mol

Description:

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable Powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Functional categories:

Tablet and capsule lubricant.

Solubility:

Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Melting point:

117–150 °C

Density:

1.092 g/cm3

Loss on drying:

46.0%

Stability and storage conditions:

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

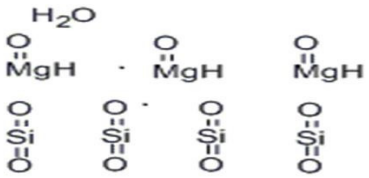
Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials.

Applications:

It is primarily used as a lubricant in capsule and tablet manufacture.

TALC

Structure:



Structural Formula:

Mg6 (Si2O5)4(OH) 4

Non proprietary names :

BP : Purified talc
JP and USP : Talc

Synonyms:

MagsilOsmanthus; Magsil Star; Powdered talc; Purified French chalk; Purtalc.

Empirical formula:

Mg6 (Si2O5)4(OH)4

Handling Precautions:

Talc is irritant if inhaled and prolongedexcessive exposure may cause Pneumoconiosis. Eye protection, gloves and respirator is

recommended.

Description:

Talc is a very fine; white to grayish-white, odorless, impalpable, unctuous, Crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Functional categories:

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Solubility:

Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Melting point: 150˚ C

Stability and storage conditions:

Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Incompatible with quaternary ammonium compounds.

Uses of talc

Use	Concentration (%)
Dusting powder	90.0–99.0
Glidant and tablet lubricant	1.0-10.0
Tablet and capsule diluent	5.0-30.0

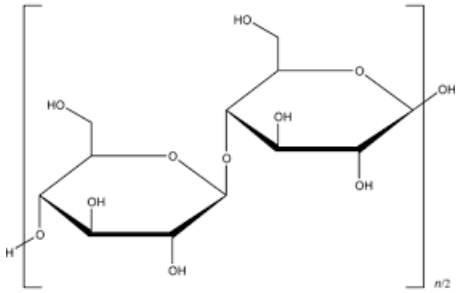
Applications:

1. It is used as a diluent, lubricant in tablet formulations.
2. In a novel powder coating for extended-release pellets and as an adsorbent.
3. In topical preparations, it is used as a dusting powder, used to clarify liquids.
4. It is also used in cosmetics and food products.

(Hand book of Pharmaceutical Excipients. Pharmaceutical Press, London.5th edition)

MICROCRYSTALLINE CELLULOSE

Structural Formula:



Synonyms:

Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur.

Empirical Formula:

(C6H10O5)n

Molecular weight:

36000g/mol

Functional Category:

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrates.

Description:

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

Solubility:

Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

pH:

pH 5.0-7.5

Melting point:

Chars at 260–2708C.

Density:

g/cm3

Incompatibilities:

Microcrystalline cellulose is incompatible with strong oxidizing agents.

Stability & Storage condition:

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Applications:

1. Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression Processes.

2. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrates properties that make it useful in tableting.

3. Microcrystalline cellulose is also used in cosmetics and food products;

Handling precaution:

Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended.

(Hand book of Pharmaceutical Excipients by Raymond C. Rowe et.al. 2009)

METHYL CELLULOSE

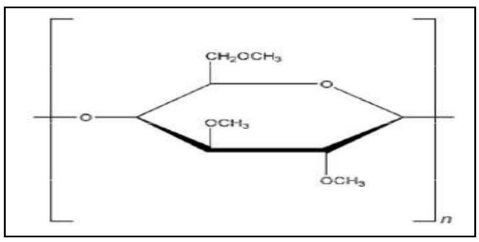
(Raymond C. Rowe *et al*., 2006)

Synonym:

Benecel

Metolose

Structure:



Empirical formula:

Long-chain substituted cellulose containing approximately 27 – 32 % of the hydroxyl group in the form of methyl ether.

Molecular weight:

10 000 – 220 000 Dalton.

Description:

Color: White, fibr ous powder or granules.

Odour: Practically odorless and

Taste: Tasteless.

Melting Point:

190–200°C.

Solubility:

Practically insoluble in acetone, methanol, chloroform, ethanol (95 %), ether, saturated salt solutions, toluene and hot water.

In cold water, it sw ells and disperses slowly to form a clear to opalescent, viscous, colloidal dispersion.

Functional Category:

- Bulk laxative (5.0 – 30.0 %).
- Emulsifying agent (1.0– 5.0 %),
- Tablet binder (1.0 – 5.0 %).
- Tablet Coating (0.5 -5.0 %).
- Tablet and capsule disintegrate (2.0 – 10.0 %).

Storage Conditions:

It should be stored in an airtight container in a cool, dry place.

Handling Precautions:

- Irritant to the eyes & eye protection should be worn.
- Methylcellulose is combustible.

- Spills of the dry powder or solution should be cleaned up immediately, as the slippery film that forms can be dangerous.

Regulatory status:

Included in the FDA inactive ingredients. Recognized by GRA S status.

ETHYL CELLULOSE

(Raymond C. Rowe *et al*., 2006)

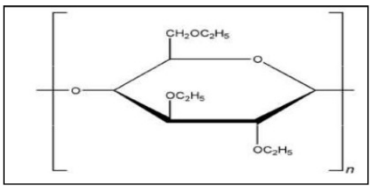
Synonyms:

Aquacoat ECD

Aqualon

Ethocel

Structure:



Empirical formula:

C12H23O6(C12H22O5)nC12H23O5

Molecular weight:

40 0000

Description:

Color: White to light tan colored powder.

Odour: Odorless.

Taste: Tasteless.

Melting point:

165^0 - 185^0 C

Solubility:

Practically insoluble in propylene glycol, glycerine and water

Freely soluble in chloroform, ethanol, ethyl acetate, methanol and toluene.

Functional Category:

- Coating agent.
- Flavouring fixativ e.
- Tablet binder.
- Tablet filler.
- Viscosity-increasi ng agent.

Storage Conditions:

It should be stored at a temperature not exceeding 328^0 C (9 0^0F) in a dry area away from all sources of heat.

Handling Precautions:

- To prevent fine dust clouds of ethyl cellulose from reaching p otentially explosive levels in the air.
- Its combustible
- It may be an irritant to the eyes and eye protection should be w orn.

Regulatory status:

Included in the FDA inactive ingredients. Recognized by GRA S status.

PVP K-30

(Raymond C. Rowe *et al*., 2006)

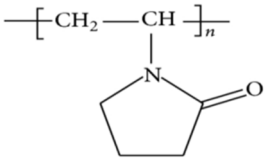
Synonyms :

Kollidone

Plasdone;

Poly[1-(2-oxo-1-pyrrolidinyl)ethylene];

Structural formula :



Nonproprietary Names:

BP: Povidone

JP: Povidone

Chemical Name and CAS Registry Number:

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Molecular weight :

50, 000

Description:

Colour: Fine, white to creamy white hygroscopic powder

Odour: Odourless

Melting point:

150^{o} C

Solubility :

Freely soluble in acids, chloroform, ethanol

Practically insoluble in ether.

Functional category :

- Disintegrant;
- dissolution enhancer;
- suspending agent;
- tablet binder

Storage Precautions:

Povidone darkens to some extent on heating at 1508C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–1308C.

Incompatibilities:

It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds.

Handling precautions:

Observe normal precautions appropriate to the circumstances andquantity of material handled. Eye protection, gloves, and a dust mask are recommended.

Regulatory status:

Accepted for use in Europe as a food additive. Included in the FDA Inactive Ingredients Database (IM and IV injections; ophthalmic preparations; oral capsules, drops, granules, suspensions tablets; sublingual tablets; topical and vaginal preparations).

Applications:

- In tableting, povidone solutions are used as binders in wet-granulation processes.
- Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions.
- Povidone is used as a solubilizer in oral and parenteral formulations, and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.

Uses	Concentration(%)
Carrier for drugs	10-25
Dispersing agent	Upto 5
Tablet binder, diluents, coating agent	0.5 - 15

CHAPTER 10

EXPERIMENTAL PROTOCOL

EXPERIMENTAL PROTOCOL

1. STANDARD CURVE FOR FEBUXOSTAT :

a) Preparation of dissolution medium

Acid buffer PH 1.2 (Indian pharmacopoeia 1996, volume: 2, page no: A-144)

Place 50ml of 0.2M potassium chloride in a 200ml volumetric flask, add the Specified volume of 0.2M hydrochloric acid and then add water to volume.

Preparation of 0.2M potassium chloride

Dissolve 14.911gm of potassium chloride in water and dilute with water to 1000ml.

Preparation of 0.2M Hydrochloric acid

Hydrochloric acid diluted with water to contain 17ml of HCl in 1000ml.

b) Estimation of absorption maximum (λ max) for Febuxostat by UV Spectroscopy

The standard stock solution of Febuxostat having concentration 1000µg/ml is prepared by dissolving 100mg of Febuxostat is dissolved in little amount of methanol and diluted with Acid buffer pH 1.2 up to 100ml. The stock solution is further diluted using acid buffer pH 1.2 to produce 10µg/ml concentration. The resultant solution is scanned between wavelengths of 200-400 nm by UV Spectrophotometer. (UV-1700 Shimadzu Corporation, Japan) to get absorption maximum (λ max).

c) Preparation of standard calibration curve for Febuxostat

From the above stock solution , aliquots are taken into different volumetric flasks and volume are made up to 100 ml with Acid buffer pH 1.2 solution, so as to get concentration of 2 to 20 µg/ml. The absorbance of these solutions are measured at 317 nm by UV Spectrophotometer. A calibration curve is plotted by taking concentration on X-axis and absorbance on Y-axis to obtain the standard curve. **(US Pharmacopeia).**

2. DRUG-POLYMER COMPATIBILITY STUDIES

The compatibility studies are carried out by Infrared spectroscopy and Differential scanning calorimetry in order to evaluate the drug polymer interaction.

a) Fourier Transform Infrared Spectroscopic studies (FTIR)

Drug- polymer/excipients interactions play a vital role in the release of drug from formulation. Fourier transform infrared spectroscopy (FTIR) has been used to study the physical and chemical interactions between drug and the excipients used. The study is carried out by KBR pellet technique. Materials are compressed under 10 tones pressure in a hydraulic press to form a homogeneous sample/KBr pellet. The pellet is scanned over the frequency range from 4000 to 450 cm-1 and peaks obtained are identified. **(Narayana Raju .P, *et al*., 2009; Solanki. D, et al., 2013)**

b) Differential scanning calorimetric studies (DSC)

The DSC measurements are performed using a Perkin Elmer Pyris (Shelton, CT) equipped with an intracooler 2P cooling accessory. Samples of 4 mg are placed in standard aluminum pans and sealed with a lid. Heating scans by 10˚C/min is applied with a nitrogen purge of 20 ml/min, over a temperature range of 35ºC to 380ºC. An empty aluminum pan is used as reference. **(Solanki. D, *et al*., 2013)**

3. FORMULATION OF FEBUXOSTAT FLOATING

TABLETS:

Preparation of solid dispersion by fusion method:

Solid dispersions of Febuxostat with PEG-6000 in different weight ratios were prepared by fusion method in three different ratios 1:1, 1:2, 1:3. PEG-6000 was melted at 60ºC and Febuxostat was added to the melted carrier and stirred continuously to form a homogenous mixture. The resulting homogenous

preparation was rapidly cooled in a freezing mixture of ice and sodium chloride, and stored in desiccators for 24 h. Subsequently, the dispersion was ground in a mortar and sieved through 100 # and stored in a dessicator.

Preparation of Hydrodynamically Balanced System of Febuxostat:

EFFERVESCENT AND NON-EFFERVESCENT TECHNIQUES

Preparation: In this work, direct compression method has been employed to prepare HBS of Febuxostat with Hydroxy propyl methyl cellulose (HPMC) of two different grades (HPMC K4M and HPMC K100M) and Methyl cellulose for Effervescent formulations and along with 10% Ethyl cellulose in case of Non-effervescent formulations.

Procedure: All the ingredients were accurately weighed and passed through mesh # 60. In order to mix the ingredients thoroughly drug and polymer were blended geometrically in a mortar and pestle for 15 minutes then sodium bicarbonate, citric acid, mcc, talc and magnesium stearate were mixed one by one. After thoroughly mixing these ingredients, the powder blend was passed through # 44 mesh.

Tablets were compressed on a tablet machine (FLUID PACK) using 10mm concave punches.

4. EVALUATION OF FEBUXOSTAT FLOATING MATRIX TABLETS

a) Pre compressional evaluation of powder blend: (Dongre *et a*l., 2015: AvaruGeetha Dutt *et al*., 2014)

i) Angle of repose

The flow characteristics are evaluated by determining angle of repose.

Improper Flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. Angle of repose is calculated using the equation.

$$\tan \theta = h/r, \quad \theta = \tan^{-1} h/r$$

Where h = height of pile

r = radius of the base of the pile θ

= angle of repose.

Angle of repose	Type of flow
<20˚	Excellent
20˚-30˚	Good
30˚-35˚	Moderate
35˚-40˚	Poor
>40˚	Very poor

ii) Bulk Density

Apparent bulk density is determined by pouring pre sieved drug excipients blend into a graduated cylinder and measuring the volume and weight “as it is”. It is expressed in g/mL and is given by, $\mathbf{Db = M / V_o}$

Where, **Db** is the bulk density, **M** is the mass of powder and $\mathbf{V_o}$ is the Bulk volume of the powder.

iii) Tapped density

It is determined by placing a graduated cylinder, containing a known mass of drug excipients blend, on mechanical tapping apparatus. The tapped volume is measured by tapping the powder to constant volume. It is expressed in g/mL.

Dt = M / Vt Where, **Dt** is the tapped density**, M** is the mass of powder and **Vt** is the tapped volume of the powder.

iv) Compressibility index (or) Carr's Index (I)

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. A material having values less than 20 to 30% is defined as the free flowing material, based on the apparent bulk density and tapped density.

The percentage compressibility of the bulk drug is determined by using the following formula **I = Dt – Db / Dt × 100**

Where, I is the Compressibility index, **Dt** is the tapped density of the powder and **Db**. is he bulk density of the powder.

Compressibility index (%)	Type of flow
10	Excellent
11-15	Good
15-20	Fair
21-25	Passable
26-31	Poor
32-37	very poor

v) Hausner's ratio

It indicates the flow properties of the powder. The ratio of Tapped density to bulk density of the powder or granules is called Hausner's ratio.

H = Dt / Db

Where, **H** is the Hausner's ratio, **Dt** is the tapped density of the powder and **Db** is the bulk density of the powder.

Hausner's ratio	Type of flow
1-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.54	very poor
>1.60	very very poor

vi) Drug content

Weight of the powder material equivalent to 40 mg of Febuxostat is taken and transferred into 100 ml volumetric flask. Then 30 ml of Acid buffer PH 1.2 is added slowly, mixed properly and the volume is made up to 100 ml with Acid buffer PH 1.2. The above solution is filtered and 10 ml of filtrate is taken into 100 ml volumetric flask and made up to final volume with Acid buffer PH 1.2 and the drug content is estimated by measuring the absorbance at λ max 317 nm using a UV-spectrophotometer.

s

b) Post compressional evaluation of floating matrix tablets: (Dongre *et al*., 2015; Jaimini M, et al., 2007)

i) General appearance

The formulated tablets are evaluated for general appearance. Viz., color, odour,

shape.

ii) Tablet Dimension

The thickness and diameter of the tablets are carried out using digital vernier caliper.

Three tablets are used from each batch and results are expressed in millimeter (mm).

iii) Weight variation test

Twenty tablets are selected at random, individually weighed in a single pan electronic balance and the average weight is calculated. The uniformity of weight is determined according to I.P. specification. As per IP not more than two of individual weights should deviate from average weight by more than 5% and none deviate more than twice that Percentage.

The following percentage deviation in weight variation is shown in the table. (**IP.2007).**

Average weight of a tablet	Percentage deviation
Less than 80mg	± 10%
More than 80mg to less than 250mg	± 7.5%
250mg or more	± 5%

iv) Hardness test

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shocks of handling in manufacture, packing and shipping. Monsanto hardness tester is used to measure the hardness of tablet. Three tablets from each batch are used for hardness test and results are expressed in Kg/cm^2.

v) Friability test

It is done in Roche friabilator apparatus where the tablets are subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm for dropping the tablets at a distance of six inches with each revolution. Pre weighed samples of 20 tablets are placed in the friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Compressed tablets that loss less than 0.5 to 1.0% of their weight are generally considered acceptable. The percentage friability is calculated by the following

$$\% \, friability = \frac{W_0 - W_f}{W_0} x100$$

vi) Drug content uniformity

Ten tablets are weighed and taken in a mortar and crushed to make powder form. A quantity of powder weighing equivalent to 40mg of drug is taken in a 100ml volumetric flask and Acid buffer PH 1.2 is added. The solution is filtered using membrane filter (0.45µm) and 10 ml of filtrate is taken into 100 ml volumetric flask and made up to final volume with Acid buffer PH 1.2. Then its absorbance is measured at 317nm using UV Visible spectrometer. The amount of drug present in one tablet is calculated using standard graph.

%Purity = Absorbance of unknown(Au)/Absorbance of standard (As)*10C,

Where, C is Concentration.

vii) In vitro floating lag time (Deepika B. *et al*., 2013)

The in vitro buoyancy was determined by floating lag time (FLT). The tablets were placed in a 250 ml beaker containing 0.1N HCl. The media was kept in stagnant condition and the temperature was maintained at 37^0 C. The time required for the tablet to rise to the surface and float was determined as floating lag time.

viii) In vitro floating duration time

The floating capacity of the tablets was determined using USP Dissolution apparatus II containing 900ml of simulated gastric fluid. The time interval between introduction of the tablet in to the dissolution medium and its buoyancy to the dissolution medium was taken as buoyancy lag time/ Total floating time(TFT) and for which time the tablet constantly floats on the surface of the medium was observed visually and taken as floating duration.

ix)Determination of Swelling Index:

Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule, breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of %

weight gain by the tablet.

Method:

For each formulation batch, one tablet was weighed and placed in a beaker containing 200 ml of buffer media. After each interval the tablet was removed from beaker and weighed again up to 12 hours. The swelling index was calculated using following formula.

Swelling Index (S.I.) = (Wt-Wo)/Wo

Where, S.I. = Swelling index

Wt = Weight of tablet at time t

Wo = Weight of tablet before placing in the beaker

ix) In vitro drug release studies: (Karthik raja .M *et al*., 2012)

`Dissolution characteristics of the formulated floating tablets of Febuxostat are carried out using USP Type II (paddle) dissolution test apparatus for 12hrs.

Method:

900 ml of acid buffer pH 1.2 was filled in dissolution vessel and temperature of the medium is set at 37°C ± 0.5°C. One tablet of different batch is placed in each dissolution vessel and the rotational speed of paddle was set at 75rpm. 5ml of sample is withdrawn at pre-determined time interval of every one hour for up to 12 hours and same volume of fresh medium is replaced immediately. The withdrawn sample is diluted to 10ml in volumetric flask and filtered through 0.45µ membrane filter. The resultant samples are analyzed for drug content at 317nm using UV-Visible spectrophotometer.

Parameter	Specifications
Dissolution Medium	Buffer 0.1N hydrochloric Acid
Temperature	37.0 ± 0.5 °C
Initial Volume	900ml
Rotation Speed	75rpm
Drawn Volume	5ml
Running Time	12 hrs. in 0.1N hydrochloric Acid

X) *IN-VITRO* DRUG RELEASE KINETICS (Reddy et. al., 2012)

To analyze the *In-vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate describes the systems where the drug release rate is independent of its concentration. The first order describes the release from the system where release rate is concentration dependent. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on the Fickian diffusion. The Hixson-Crowell root law describes the release from the systems where there is a change in surface area and diameter of particles. The Koresmeyer-peppas describes the mode of release of drug from swell able matrices.

Release Kinetics Model	Equation
Zero Order	$Qt = Q_0 + K_0.t$
First Order	$In\ Qt = In\ Q_0 + K_0.t$
Hixson-Crowell	$Q_0 1/3 – Qt\ 1/3 + K.t$
Higuchi	$Q = KH.\ t1/2$
Korsmeyer – Peppas	$Mt / M_0 = a.tn$

Fitness of release profiles to linear equations is assessed by comparing the coefficients of determination (r) values. **(Harris Shoaib *et al*., 2006: Praveen Kumar Mandapali *et al*., 2012).**

Diffusion exponent values indicating drug release mechanism

S. No.	Diffusion exponent value (n)	Drug release mechanism
1	< 0.5	Fickian release
2	0.5 to 1.00	Non-Fickian transport
3	1.00	Case II transport
4	> 1.00	Super case II transport

The *in-vitro* release data are fitted to the above mathematical models and the applying data are,

- Cumulative % drug release vs. time for zero order kinetic.
- Log cumulative of % drug remaining vs. time for first order kinetic.
- Cumulative % drug release vs. Square root of time for Higuchi model.
- Log cumulative % drug release vs. log time for Korsmeyer-Peppas model and
- Cube root of drug % remaining in matrix vs. time for Hixson-Crowell cube root time.

xi) Selection of best formulation:

The best formulation is selected in accordance with the results obtained from floating behavior, swelling index, invitro drug release studies and kinetic analysis.

xii) Evaluation of selected best formulation:

a) Infrared spectroscopic studies:

The interaction between the drug and excipient / polymer are studied by FT-IR as per the procedure as mentioned in 2(a).

(b) Differential scanning calorimetric studies (DSC):

Differential scanning calorimetry is carried out to find out any incompatibility between the drug and excipients used.

c) Powder X-Ray Diffraction Method:

Powder X-Ray diffraction method is carried out to find out the crystalline nature of drug through out the formulation.

Comparison with marketed Formulation:

The release of the best formulation is compared with the marketed formulation **(Pare A *et al*., 2008: Mahajan P *et al*., 2011).**

***In vivo* x – ray studies:**

The *in vivo* studies approved by Institutional Animal Ethical Committee and are performed on healthy albino rabbit weighing 2-2.5 kg. The animal is fasted overnight but allowed to take water ad libitum (Londhe S *et al*., 2010). Then 30 ml of 5 % dextrose solution is given immediately before administering the tablets by using stomach tube (No. 12 French Catheter) and 20 ml syringes.

The tablets are made opaque by incorporating barium sulphate (BaSO4) instead of drug. The rabbit is exposed to X-ray imaging in the abdominal region, and photographs are taken at 0, 2, 4, 6, 8, 10 & 12 hrs. After administration of tablet. At hourly intervals 30 ml of 5% dextrose solution is given to maintain optimum fluid level in the stomach (Dinesh Kumar *et al*., 2010). The gastric residence time is observed.

STABILITY STUDIES

Stability studies were carried out by using selected formulation i.e F4. The formulation is kept in accelerated stability condition at 40^{0C} temperature 75 ± 5% relative humidity for a period of 2 months as per International Conference on Hormonization guidelines (Mathews, 1999; International Conference on Harmonization Steering Committee,1999).The samples were withdrawn at every 15 days intervals and evaluation was carried out for appearance, thickness, hardness, buoyancy lag time, drug content and *In-vitro* release studies (60 days).

CHAPTER 11

RESULTS AND DISCUSSIONS

RESULTS AND DISCUSSION

1.STANDARD CALIBRATION CURVE FOR FEBUXOSTAT:

a) Preparation of dissolution medium2

The dissolution medium was prepared by using Acid buffer PH 1.2.

(Indian pharmacopoeia 1996, volume: 2, page no: A-144)

Estimation of absorption maximum (λ max) for by Ultraviolet Spectroscopy(UV)

The absorption maximum (λ max) of Febuxostat was estimated by scanning the drug solution (10µg/ml) between 200-400nm regions on UV spectrophotometer. The obtained spectrum showed that the absorption maximum (λ max) was 317 with Acid buffer PH 1.2.

The result was shown in **Fig.1.**

b)Preparation of standard calibration curve for Febuxostat

The standard calibration curve for Febuxostat was prepared by using acid buffer PH 1.2. The absorbance was measured at λ max of 317nm.The correlation coefficient was found to be 0.99976 , which indicate linearity. Febuxostat obeys beer's law within the concentration range of 2 - 20µg/ml. Calibration plot of Febuxostat in acid buffer was shown in **Table.1 & Fig.2.**

2.DRUG-POLYMER COMPATIBILITY STUDIES

a)Fourier Transform Infrared Spectroscopic studies (FT-IR)

Infrared spectroscopic analysis was performed to check out the compatibility between the drug (Febuxostat) and the hydrophilic polymers (HPMC K4M, HPMC K100M,) and Methyl cellulose, hydrophobic polymer (Ethyl cellulose) used in the

formulation of floating matrix tablets. IR spectrum of the pure drug and the physical mixtures of drug with polymers of optimized formulation were studied. The results were shown in the **Fig 3A-D.** Mixtures of drug and polymers showed that there was no shifting of functional peaks.

THE FT-IR SPECTRA OF PURE DRUG FEBUXOSTAT

S.NO.	Functional group	Peak in cm^{-1}	Peak observed (cm^{-1})
1	-NH_2 streching	3539.41-3462.95	3462.22
2	C=O Stretching (Carboxylic acid)	1670	1678.07
3	OH-C Stretching	1375.61	1382.96
4	C-C Stretching (Aromatic ring)	1455-1592	1467.83
5	C-H stretching (alkanes)	2957.68	2939.52
6	N-C Stretching	1603.25	1604.77

All the major peaks present in the spectrum of pure drug were clearly observed in the spectrum of physical mixtures with negligible changes. The obtained results clearly showed that there was no interaction between the drug and polymers.

b)Differential Scanning Calorimetric (DSC) Studies

The DSC studies were carried out to detecting the drug- polymer incompatibility. Febuxostat exhibits a sharp endothermic peak at 192^0 C. An endothermic peak corresponding to the melting point of pure drug was prominent in all the drug polymer mixture, which suggested clearly that there was no interaction between the drug and polymer and the drug was existed in its unchanged form. The results were shown in **Figure4 A-B.**

3.FORMULATION OF SUSTAINED RELEASE FLOATING MATRIX TABLET

FORMULATUION OF SOLID DISPERSION: The solubility of FEBUXOSTAT is enhanced by preparing solid dispersion using PEG6000 in the (1:1,1:2, 1:3) ratios by melting method and comparing the results with pure drug and marketed formulation. **Table 2-5, Figure 6A-C.**

EFFERVESCENT TECHNIQUE

The Febuxostat floating tablets were prepared by effervescent technique used the hydrophilic polymers (HPMC K4M, HPMC K100M,) and Methyl cellulose. Sodium bi carbonate & citric acid used as gas generating agent. The polymers were chosen as they are well established in the similar studies and have great swelling and sustained release properties respectively. From the trial studies, the formula was optimized depending on the floating behavior of the tablets and the optimized formula was shown in the **Table 6A.**

NON –EFFERVESCENT TECHNIQUE

The tablet excipients and polymers were chosen after comprehensive drug-polymers interaction studies. The floating tablets of Febuxostat were prepared by

direct compression method. Accurately weighed quantities of drug, Hydrophilic polymers (HPMC K4M, HPMC K100M) , Methyl cellulose, hydrophobic polymers (ethyl cellulose) and Microcrystalline cellulose were manually blended homogenously in a mortar; the powderblend was passed through sieve no.22, and adequately lubricated with talc and magnesium stearate. It was then compressed into10mm biconvex tablets by using a multi punch tablet machine. and the optimized formula was shown in the **Table 6B.**

4.EVALUATION OF FEBUXOSTAT FLOATING SUSTAINED RELEASE MATRIX TABLETS

A) Pre compressional evaluation of powder blend:

(Lingaraj S.danki et al.,2010)

Effervescent technique and Non-Effervescent technique

The powder blend of all the formulations were evaluated for the pre compression parameters such as Angle of repose, Bulk density, Tapped density, Compressibility index, and Hausner's ratio**.** The results were shown in **Table 7A-B.**

i) Angle of repose (θ)

The angle of repose was used to determine the flow properties of powder blend. The angle of repose of the formulations ranged from **27˚.38' to 31˚.78'**.The results indicated that the formulations with the diluents exhibited good flow properties .The results of angle of repose for all the formulations were shown in **Table 7A-B** and **FIG. 7A**.

ii) Bulk density (gm/ml)

The bulk density is used as an index of the ability of the powder to flow. The bulk density of the formulations was in the range of **0.76 – 0.82 g/cm3.** The values of bulk density showed that the blend was not tightly packed and indicated good flow properties for coprocessed and organic diluents . The results of bulk density for all the formulations were shown in **Table 7A-B** and **FIG. 7B**

iii) Tapped density (gm/ml)

The tapped density was used to access the free flowing properties of powder blend. The tapped density of the formulations were in the range of **0.78-0.88 g/cm^3**. The results of tapped density for all the formulations were shown in **Table 7A-B** and **FIG.7C.**.

iv) Compressibility index (%)

The Carr's compressibility index was used to access the free flowing properties of powder blend. The compressibility index of all the formulations ranged from **11.92 -18.57%.** indicates that the powder has a good flow property and good propensity of compression shown in **Fig:7D.**

v) Hausner's ratio

The Hausner's ratio was an indirect index of ease of powder flow. The Hausner's ratio of all the formulations ranged from **1.12-1.20**. This indicates better flow property of blend. The results of Hausner's ratio for all the formulations were shown in **Table 7** and **FIG.7E**.

vi) Drug content (%)

The percentage drug content of formulations (F1-F9) was found to be in

between 97.18 – 98.18% and (G1 – G9) was found to be between **98.12 – 99.23%** ensured the uniformity of drug content. The results were shown in **Table 7** and **Fig.7F.**

B) Post compressional evaluation of floating matrix tablets:

(Sucharitha. M et al., 2013)

Effervescent and Non-Effervescent technique

Tablets of different formulations were subjected to evaluation tests such as general appearance, tablet dimension, hardness, friability, weight variation, drug content. The results were shown in the **Table9A & 9B.**

i) General appearance

The formulated tablets were **off-white in colour, biconvex and round shaped** without any scoring on both sides. All the tablets were elegant in appearance.

ii) Tablet dimension

The thickness and diameter of all formulations were found to be in between **4.36 to 4.49mm & 10.3mm** respectively, indicates that the tablets having uniform particle size distribution and no deformity. The results were shown in the **Table9A & 9B.**

iii) Hardness

The hardness of all formulations were found to be in between **4.76 to 5.12kg/cm^2** which indicates good mechanical strength with an ability to withstand physical and chemical stress conditions while handling. The results were shown in the **Table9A & 9B.**

iv)Friability

The friability of all formulations were found to be in between **0.356 to 0.395 %,** (as per I.P Limit is less than 1%), which indicates good mechanical resistance of the tablet. The results were shown in the **Table9A & 9B.**

v) Weight variation

In all the formulations, the weight variation of floating tablets was ranges between **348.92-351.7mg**. All the formulated tablets were passed the weight variation test as the % weight variation was within the pharmacopoeia limits of ±7.5% of the average weight, which proved good uniformity. The results were shown in the **Table9A & 9B.**

vi)Estimation of drug content

The percentage drug content of formulations (F1-F9) was found to be in between **97.18 – 98.18%** and (G1 – G9) was found to be between **98.12 – 99.23%** ensured the uniformity of drug content. which is within acceptable limits, showed that the drug was uniformly distributed in all formulations. Hence the percentage of drug content of all formulations complies with official specifications as per I.P (Limits: not less than 85% and not more than 115%). The results were shown in **Table9A & 9B.** And **Fig.7F.**

***vii)IN VITRO* BUOYANCY TEST (CHANDRA SEKHARA RAO. ET AL., 2011)**

The prepared tablets were subjected to *in vitro* buoyancy test by placing them in 250 ml beaker containing 200 ml of 0.1 N HCl (pH 1.2, temp. 37±0.5ºC). The time between introduction of the dosage form and its buoyancy in the medium and the floating durations of tablets was noted for the determination of lag time and total buoyancy time by visual observation. The Time taken for

dosage form to emerge on surface of medium is called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time the dosage form remained buoyant is called Total Floating Time (TFT). The result were shown in the **Table 11A-11B** and **Figure 8A.**

EFFERVESCENT

The floating lag time may be explained as a result of the time required for dissolution medium to penetrate the tablet matrix and develop the swollen layer.(**Garg Shiv Kumar *et al.,*2011).**

The formulations containing HPMCK4M, **F1-F3 (10 %(49sec), 20%(52sec), 30%(48sec), HPMC K100M, F4-F6 (10%(23sec),20%(35sec) and 30%(39sec), Methyl cellulose, F7-F9(10% (95),20%(106sec), 30%(89sec))** floats in Medium of acid buffer. **TABLE 11A.**

NON-EFFERVESCENT

The tablet floating lag time (FLT) was found to be less than 203sec and total floating time up to 12hr. The floating lag time may be explained as a result of the imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. The formulations containing **HPMCK4M, G1-G3 (20 %(302sec), 30%(296sec), 40%(305sec), HPMC K100M, G4-G6 (20%(198sec),30%(155sec) and 40%(203sec), Methyl cellulose, G7-G9(20% (504),30%(512sec), 40%(621sec))** floats in Medium of acid buffer. All the formulations contained 10% of Ethyl cellulose as buoyancy increasing agents. **TABLE 11B.**

Effervescent formulation: (Narang *et al.,* 2011)

The combination of sodium bi carbonate and citric acid provided desired

floating ability and therefore this combination was selected for the formulation of the gastro retentive tablets. The gas generated is trapped and protected within the gel formed by hydration of the polymer (HPMC), thus decreasing the density of the tablet below 1gm/ml, and the tablet becomes buoyant. HPMCK100M showed delayed floating lag time as compared with other excipients due to its higher viscosity owing to more polymer entanglement and gel strength.

Non-effervescent formulation: (Ravi kumar *et al.,* 2009)

With reference to buoyancy studies results it can be concluded that the batch containing HPMC polymers and its combination with ethyl cellulose showed good floating lag time. The buoyancy of the tablet varies from polymer to polymer which is governed by both the swelling of the hydrocolloid upon contact with the dissolution fluid and the presence of voids in the centre of the tablet **(Ramesh C. Nagarwal *et al.*, 2010).** The formulation containing **F5(HPMCK100M)** floated within **35sec** whereas the minimum floating lag time for the non-effervescent formulations is **G5 (155 sec).**

viii) SWELLING INDEX STUDIES: (LINGARAJ S.DANKI ET AL., 2010: NAYAK

R.K *et al.*,2011) **TABLE 10A-11B.**

Effervescent formulations: .

The formulation containing HPMC K4M F1-F3 (10%,20%,30%) showed the swelling index of 12 hours **76.91%, 78.51%, 76.82%.** The formulations containing HPMC K100M, F4-F6 (10%,20%,30%,) showed the swelling index of **80.57%, 89.56%, 87.24%,).** The formulations containing Methyl cellulose,

F6-F9 (10%,20%30%) showed the swelling index of **(71.97%,72.64%,70.50%).** From the above results, the overall swelling index was found to be in the following order **HPMC K100M > HPMC K4M > Methyl cellulose** were shown in **TABLE 11A and Fig 7G.**

Non-effervescent formulations: .

The formulation containing HPMC K4M G1-G3 (10%,20%,30%) showed the swelling index of 12 hours **70.35%, 73.51%, 66.69%.**The formulations containing HPMC K100M, G4-G6 (10%,20%,30%,) showed the swelling index of **75.23%, 72.23%, 70.24%,).** The formulations containing Methyl cellulose, G6-G9 (10%,20%30%) showed the swelling index of **(71.5%,68.04%,74.25%).** From the above results, the overall swelling index was found to be in the following order,

HPMC K100M > HPMC K4M > Methyl cellulose were shown in **Fig 7G.**

The in-vitro Swelling index of formulation containing **F5** (HPMC K100M-89.56%) and **G4** (HPMCK100M-75.23) showed that highest swelling index compared to all other formulations. The results were shown in the **Table 11B.**

Effect of hydrophilic and hydrophobic polymers on swelling index:

It was observed that, the tablets containing combination of both hydrophilic and hydrophobic polymers having less swelling index than that of the formulations containing hydrophilic polymers alone. This could be due to the less permeability of water into the hydrophobic polymer, which minimized the swelling of the matrix tablets **(Doddayya *et al*., 2011).**

Among all the 18 formulations, **F5(HPMC K100M)** ,**figure 8B** formulation showed the maximum swelling index of 89.56% at the end of 12hours, due to

high viscosity and high water retention property of HPMC K100M. The viscosity of the polymer had a major influence on swelling process and matrix integrity. It was concluded that, there exists a linear relationship between swelling process and polymer viscosity **(Margret Chandira R *et al*., 2010; Deshbhratar R. M. *et al*., 2010; Praveen Kumar Mandapalli *et al*., 2012).**

ix) *IN VITRO* RELEASE STUDIES:

In vitro dissolution studies of all the formulations of floating tablets of **Febuxostat** were carried out in Acid buffer (0.1 N HCl). The study was performed for 12 hrs, and cumulative drug release was calculated at different time intervals.

Effects of various ingredients and their concentration on drug release were studied. It was observed that the type of polymer influences the drug release pattern. **(F1 to F9)** and **(G1 to G9)** . **(Jinal Patel et al., 2012).**

The *in-vitro* drug release profiles for the formulations **(F1-F9)** and **(G1-G9)**were tabulated in **Table.12A-13B.** The plot of cumulative drug release (vs) time (hr) was plotted (F1-F9) and depicted as shown in **Fig.14A-14D.**

Effervescent formulations: TABLE 12A.

In vitro drug release studies of formulations containing HPMC K4M (F1-F3) (20%,30%, 40%,) showed the drug release of **75.3%, 74.6%, 73.6 %** at the end of 12hrs respectively. In vitro drug release studies of formulations containing HPMC K100M (F4- F6) (20%,30%, 40%,) showed the drug release of **71.8%, 68.31 %, 85.8 %,** at the end of 12hrs respectively. In vitro drug release studies of formulations containing Methyl cellulose (F7- F9) (20%,30%, 40%,) showed the drug release of **84.2 %, 83.7 %, 82.0 %,** at the end of 12hrs respectively.

Sustained release profiles were observed in the following order,

HPMC K100M > HPMC K4M > Methyl cellulose

irrespective of the type of polymer. This was due to the high viscosity of the polymer (HPMC K100M) than the others. The high viscosity grades induce the formation of strong viscous gel layer when they come in contact with the aqueous media that slowed down the rate of diffusion of medium into the tablet, which may results in the retardation or decrease the drug release. **(Anilkumar J. Shinde *et al*., 2010; Margret Chandira R *et al*., 2010; Amit Kumar Nayak *et al*., 2011; Ramesh C. Nagarwal *et al*., 2010).**

Non-effervescent formulations: TABLE 12B.

In vitro drug release studies of formulations containing HPMC K4M (G1-G3) (20%,30%, 40%,) showed the drug release of **85.2%,89.6%, 92.6 %** at the end of 12hrs respectively. In vitro drug release studies of formulations containing HPMC K100M (G4- G6) (20%,30%, 40%,) showed the drug release of **77.7 %, 90.9 %, 89.7 %,** at the end of 12hrs respectively. In vitro drug release studies of formulations containing Methyl cellulose (G7- G9) (20%,30%, 40%,) showed the drug release of **88.2 %, 87.5 %, 86.8 %,** at the end of 12hrs respectively.The drug release retarded in the following order,

HPMC K100M & EC > HPMC K4M & EC > MC & EC

Ethyl cellulose is hydrophobic in nature, which restricts the penetration of dissolution medium inside the matrix and also restricts the formation of gel layer around the matrix. So that, the drug release from the hydrophobic matrix decreased as compared to the hydrophilic polymers. Nearly all the formulations

showed a drug release .Hence, it was concluded that the floating matrix tablets prepared with effervescent techniques exhibited better drug release properties. Among all the formulations, F5 (HPMC K100M-20%) is choosen as the best formulation on the basis of *in vitro* drug release, floating lag time, total floating time and swelling index. It showed maximum drug release in a sustained release manner **(68.03% in 12hrs)** because the formation of strong viscous gel layer that slowed down the rate of diffusion of medium into the tablet. The results are shown in **TABLE13A-13B** and **FIGURE 9A-9F.**

x) INVITRO RELEASE KINETICS STUDIES:

To analyze the release mechanism as well as to select the formulation for *in vivo* studies, the *invitro* release data were fitted into various release equations and kinetic models (zero order, first order, Higuchi, Hixson-Crowell, Korsemeyer-Peppas).

The release kinetic data for all the formulations were shown in the T able: **14A &14B & Figure: 10A-1-10E-6.**The kinetic studies of all the formulations showed that zero ord er plots were fairly linear as indicated by their high regression values. Therefore it was ascertained that the drug release from all the formulations followed zero order kinetics **(Regression coefficient values (R^2) between 0.938 – 0.991) (Praveen Kumar Mandapalli *et al*., 2012).**

Diffusion is related to the transport of drug from the dosage form into the *invitro* study fluid depending on the concentration **(Ravikumar *et al.,* 2009).** This was explained by Higuchi's model. The release profiles of drug from all the formulations could be best expressed by Higuchi's equations **(Amit**

Kumar Nayak *et al*., 2011), as the plot showed high linearity with regression coefficient values (R^2) between **0.939 – 0 .996.**

The kinetic data of all the formulations showed good fit in Korsmeyer equation which showed the combined effect of diffusion and erosion mechanism for controlled drug release. By using Korsmeyer-peppas model, if **n= 0.45** it indicates Fickian diffusion controlled drug release (Mina Ibrahim Tadros *et al*., 2010), if **n=0.89** it indicates swelling controlled drug release, if n values between 0.45 to 0.89 can be regarded as an indicator for both the phenomena (Anomalous transport or Non-Fickian diffusion) **(Ramesh C. Nagarwal *et al*., 2010; Amit Kumar Nayak *et al*., 2011; Praveen Kuma r *et al*., 2011)**.

It was found that the mechanism for all formulations were Anomalous Non-Fickian diffusion (the release from initially dry, hydrophilic glassy polymers that swell when added to water and become rubbery show anomalous diffusion as a result of the rearrangement of macromolecular chains) **(Sasa Baumgartner *et al.,* 2000).**

xi)SELECTION OF BEST FORMULATION:

From the above results, F5 was selected the best formulation based on following character,

- Floating lag time : 35 seconds.
- Total floating time : up to 18hrs.
- swelling index : 89.56 % (12hrs).
- *In-vitro* release profile : 68.03% (12hrs).
- . *In-vitro* release kinetics : Zero order kinetics (r^2= 0.991).

xii)EVALUATION OF BEST FORMULATION:

A)Infrared spectroscopy:

IR spectrum of the best formulation **F5 (HPMC K100M-20%)** was recorded and shown in the **Fig11**. Pure Febuxostat spectra showed sharp characteristic peaks represented below..All the below characteristic peaks appear in the IR spectrum of best formulation which indicates that there was no modification or interaction between drug and polymers.

B) Differential Scanning Calorimetric (DSC) Studies:

DSC thermogram of the best formulation **F5 (Febuxostat, HPMC K100M**) were recorded. Pure Febuxostat exhibits a sharp endothermic peak at **210^{0}C.** (**Figure 4A).** The peaks observed after solid dispersion technique is **70.0, 206.1.**
An endothermic peak corresponding to the melting point of pure drug was prominent in best formulation (F5) **(Figure 12)**, (**192.11^{0}C,65.95^{0}C, 56.45^{0}C,)** which suggested clearly that there was no interaction between the drug and the polymers and the drug was existed in its unchanged form.

C)Powder x-Ray Diffraction study(PXRD):

The XRD technique was performed to evaluate the physical characteristics of the active ingredient. This method is usually used to determine the physical characteristics of drugs and polymers, and can therefore investigate whether a drug is molecularly dispersed in tablet or drug is changed as an ionic interaction. Also, the presence of polymers (indicated by some small sharp peaks) suggests that the polymer structure is crystalline or semi-crystalline. XRD studies of the pure drug has peaks at 11.7, 12, 14.5, 15.9, 17.6, 24.3. XRD of pure drug with

PEG6000 gave peaks at 12.8, 14.4, 16.9, 23.4, 24.6. The peaks for the best formulation gave 11.6,12.9, 14.4, , 20.8, 25.9. Thus, it can be concluded that, compared with all figures, the drug is present in the formulation and has a less crystalline character as it is evident from the graph that it has less sharp peaks as compared with Pure drug and SD. The results are shown in **Figure: 5A, 13.**

D)Comparison of Marketed formulation with best formulation:

The promising formulation **(F5)** as found by evaluation studies was compared with marketed formulation.The Cumulative % drug release of the best formulation **(F5)** was found to be 68.03% in 12hours when compared to the tablet whose cumulative % drug release was 98.2% in hours.Thus the formulation **F5** showed sustained release profile than the marketed tablet. The results were shown in **Figure: 14.**

***E)IN-VIVO* X-RAY STUDIES:**

Based on the results obtained after performing physicochemical characteristics, In- vitro buoyancy, In vitro drug release and swelling index, among all formulations, F5 containing HPMC K100M polymer have shown best and satisfactory results. Hence, this formulation was selected for further *In vivo* evaluations.

The *in-vivo* x-ray studies were carried out after getting clearance from Institutional Animal Ethical Committee. X-ray studies were conducted to find out the gastric retention of tablet.

The *in-vivo* radiographic studies were performed in healthy male albino rabbit at periodic time intervals (0, 2, 4, 6, 8, 10 & 12hrs) using x-ray machine. The

appearance of the tablet in the upper part of the stomach confirms its in-vivo floating behaviour. The Change in position of the formulations in the 2nd hour x-ray and 4th hour x-ray proves that they does not adhere to the mucosa and remains floating. Also the swelling of the tablet can be visualized from the increase in its size when compared to 2^{nd} hrs. 4^{th} hrs. 6^{th} hrs. 8^{th} hrs. 10^{th} hrs. & 12^{th} hrs. X-rays. The results were shown in **Fig 15.**

F) EVALUATION OF STABILITY STUDIES FOR THE BEST FORMULATION (F5)

Stability studies were carried out for the best formulation (F5). The formulation is kept in accelerated stability condition at 40^{0C} temperature 75 ± 5% relative humidity for a period of 2 months as per International Conference on Harmonization guidelines (Mathews, 1999; International Conference on Harmonization Steering Committee,1999).The samples were withdrawn at every 15 days intervals and evaluation was carried out for appearance, thickness, hardness, buoyancy lag time, drug content and *In-vitro* release studies (60days). The result were shown in**Fig16A-D&Table15.**

CHAPTER 11

TABLES AND FIGURES

TABLE 1: CALIBRATION OF FEBUXOSTAT BY USING ACID BUFFER OF Ph1.2

CONCENTRATION	ABSORBANCE
2	0.058±0.010
4	0.121±0.016
6	0.179±0.022
8	0.238±0.031
10	0.301±0.045
12	0.353±0.051
14	0.411±0.048
16	0.469±0.060
18	0.528±0.058
20	0.601±0.062

n=3* **Regression Value – 0.99976**

TABLE 2: COMPOSITION OF SOLID DISPERSION

S.NO	Formulation code	Method	Ratio	Composition
1	A1	Melting	1:1	Drug : PEG6000
2	A2	Melting	1:2	Drug : PEG6000
3	A3	Melting	1:3	Drug : PEG6000

TABLE 3 : PERCENTAGE YIELD AND DRUG CONTENT OF SOLID DISPERSION

S.no	Formulation Code	Method	Ratio	Percentage of yield ± SD	Drug content ± SD
1	A1	Melting	1 : 1	87.09±0.01	95.38 ± 0.20
2	A2	Melting	1 : 2	88.21±0.16	96.61 ± 0.07
3	A3	Melting	1 : 3	94.75±0.03	98.55 ± 0.80

n=3*

TABLE 4: CUMULATIVE PERCENTAGE OF DRUG RELEASE OF PHYSICAL MIXTURE OF FEBUXOSTAT WITH PEG6000.

Time (min)	Percentage of drug release ± SD				
	A1 1 :1	A2 1 :2	A3 1:3	MARKETED FORMULATION	PURE DRUG
10	11.9 ±1.87	22.4 ±1.95	31.2 ± 2.08	13.6±2.55	9.16±2.97
20	19.5± 2.47	31.8 ±2.71	38.5 ± 3.05	24.5±0.007	19.25 ±0.95
30	29.1 ±1.18	39.5 ± 3.05	47.2 ± 2.78	29.5±1.25	29.34±3.06
40	34.2 ±1.08	43.2 ± 2.49	54.9± 2.3	33.8±1.28	36.71 ±1.75
50	41.4 ±1.54	51.9 ± 1.52	61.8 ± 2.54	46.4±2.57	42.4 ±3.27
60	44.5 ±2.48	59.4 ± 2.24	67.2 ± 2.78	53.6±3.08	49.1 ±1.70

n=3*

TABLE 4: CUMULATIVE PERCENTAGE OF DRUG RELEASE OF FEBUXOSTAT WITH PEG6000 AFTER SOLID DISPERSION BY MELTING METHOD

Time (min)	Percentage of drug release ± SD				
	A1 1 :1	A2 1 : 2	A3 1:3	MARKETED FORMULATION	PURE DRUG
10	26.7 ±1.66	31.1 ± 2.42	42.9±1.25	13.6±2.55	9.16±2.97
20	33.7 ±3.36	39.2 ± 1.40	50.6 ± 1.42	24.5±0.007	19.25 ±0.95
30	43.7 ±2.70	46.2 ± 1.63	64.4±3.39	29.5±1.25	29.34±3.06
40	47.9 ±2.04	51.4 ± 2.08	74.8 ± 4.05	33.8±1.28	36.71 ±1.75
50	54.1 ±2.37	58.8 ± 2.97	86.9 ± 3.15	46.4±2.57	42.4 ±3.27
60	59.4 ±2.50	66.7 ± 3.37	92.9 ± 1.82	53.6±3.08	27.1 ±1.70

n=3*

TABLE 6A:FORMULATION OF EFFERVESCENT FLOATING SUSTAINED RELEASE MATRIX TABLET

Quantity (mg) for I tablet (Average weight -350mg)

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
SOLID DISPERSION IN 1:3 RATIO (mg) [CONTAINING 40 MG FEBUXOSTAT]	160	160	160	160	160	160	160	160	160
HPMC K4M (mg)	35	70	105						
HPMC K100M (mg)				35	70	105			
METHYL CELLULOSE (mg)							35	70	105
PVP K30 (mg)	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5
SODIUM BICARBONATE (mg)	35	35	35	35	35	35	35	35	35
CITRIC ACID (mg)	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5
MCC (mg)	78	43	8	78	43	8	73	43	8
MAGNESIUM STEARATE (mg)	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
TALC (mg)	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
TOTAL WEIGHT OF EACH TABLET (mg)	350	350	350	350	350	350	350	350	350

TABLE 6B--FORMULATION OF NON- EFFERVESCENT FLOATING SUSTAINED RELEASE MATRIX TABLETS

Average Weight 200mg / Tablet

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
SOLID DISPERSION IN 1:3 RATIO (mg) [CONTAINING 40 MG FEBUXOSTAT]	160	160	160	160	160	160	160	160	160
HPMC K4M (mg)	70	105	140						
HPMC K100M (mg)				70	105	140			
METHYL CELLULOSE (mg)							70	105	140
ETHYL CELLULOSE (mg)	35	35	35	35	35	35	35	35	35
MCC (mg)	78	43	8	78	43	8	78	43	8
MAGNESIUM STEARATE (mg)	3.5	3.5	3.5	3.5	3.5	3.5	35	3.5	3.5
TALC (mg)	3.5	3.5	3.5	3.	3.5	3.5	3.5	3.5	3.5
TOTAL WEIGHT OF EACH TABLET (mg)	350	350	350	350	350	350	350	350	350

TABLE 7A- PRECOMPRESSIONAL EVALUATION OF POWDER BLEND (EFFERVESCENT TECHNIQUE)

S.no	Formulation code	Angle of repose ± SD	Bulk density (gm/ml)± SD	Tapped density (g/ml) ± SD
1	**F1**	28 ^{0}47' ± 0.5	0.736± 0.01	0.84 ± 0.02
2	**F2**	29^{0}19' ± 0.49	0.777 ±0.01	0.87 ± 0.011
3	**F3**	25^{0}84' ± 0.65	0.80 ± 0.02	0.91 ± 0.035
4	**F4**	30^{0}57' ± 1.56	0.764 ± 0.02	0.84 ± 0.02
5	**F5**	31^{0}09' ± 1.87	0.721 ± 0.03	0.87± 0.023
6	**F6**	29^{0}34' ± 0.98	0.827± 0.01	0.94 ± 0.034
7	**F7**	31^{0}10' ± 0.51	0.914 ± 0.01	1.03 ± 0.02
8	**F8**	25^{0}58' ± 1.55	0.775 ± 0.02	0.89 ± 0.02
9	**F9**	28^{0}72' ± 1.35	0.784 ± 0.03	0.94 ± 0.025

n=3*

TABLE 7B- PRECOMPRESSIONAL EVALUATION OF POWDER BLEND (NON-EFFERVESCENT TECHNIQUE)

S.no	Formulation code	Angle of repose ± SD	Bulk density (gm/ml)± SD	Tapped density (g/ml) ± SD
1	**G1**	27 ^{0}08' ± 0.5	0.747 ± 0.01	0.87 ± 0.02
2	**G2**	29^{0}53' ± 0.49	0.754 ± 0.01	0.88 ± 0.011
3	**G3**	28^{0}24' ± 0.65	0.674 ± 0.02	0.78 ± 0.035
4	**G4**	29^{0}54' ± 1.56	0.725 ± 0.02	0.86 ± 0.02
5	**G5**	30^{0}26' ± 1.87	0.871 ± 0.03	1.08± 0.023
6	**G6**	28^{0}50' ± 0.98	0.768± 0.01	0.94 ± 0.034
7	**G7**	28^{0}34' ± 0.51	0.684 ± 0.01	0.76 ± 0.02
8	**G8**	28^{0}35' ± 1.55	0.789 ± 0.02	0.95± 0.02
9	**G9**	28^{0}24' ± 1.35	0.725 ± 0.03	0.88 ± 0.025

n=3*

TABLE 8A- PRECOMPRESSIONAL EVALUATION OF POWDER BLEND (EFFERVESCENT TECHNIQUE)

S.no	Formulation Code	Compressibility index(%) ±SD	Hausners ratio (HR)±SD
1	**F1**	13.09 ± 2.74	1.15 ± 0.03
2	**F2**	11.49 ± 0.24	1.12 ± 0.31
3	**F3**	12.08 ± 1.55	1.13 ± 0.05
4	**F4**	13.69± 2.09	1.10 ± 0.03
5	**F5**	17.24 ± 2.23	1.20± 0.05
6	**F6**	12.76 ± 0.15	1.14 ± 0.01
7	**F7**	11.26 ± 1.08	1.13 ± 0.01
8	**F8**	13.48 ± 1.96	1.15 ± 0.32
9	**F9**	17.02 ± 0.52	1.20 ± 0.14

n=3*

TABLE 8B- PRECOMPRESSIONAL EVALUATION OF POWDER BLEND (NON-EFFERVESCENT TECHNIQUE)

S.no	Formulation code	Compressibility index(%) ±SD	Hausners ratio (HR)±SD
1	**G1**	14.94 ± 0.32	1.17 ± 0.05
2	**G2**	14.77 ± 0.15	1.17 ± 0.33
3	**G3**	14.10± 1.41	1.16 ± 0.02
4	**G4**	16.27 ± 2.06	1.19 ± 0.03
5	**G5**	19.44 ± 2.03	1.24 ± 0.05
6	**G6**	19.14 ± 0.14	1.23 ± 0.05
7	**G7**	10.52 ± 1.02	1.11 ± 0.09
8	**G8**	17.89 ± 1.45	1.21 ± 0.32
9	**G9**	18.18 ± 0.23	1.22 ± 0.04

n=3*

TABLE 9A-POSTCOMPRESSIONAL EVALUATION OF FEBUXOSTAT FLOATING SUSTAINED RELEASE MATRIX TABLET (EFFERVESCENT TECHNIQUE)

S.no	Formulation code	Hardness Kg/cm^2	Friability (%) ± SD	Drug content (%)± SD
1	**F1**	4.26 ±0.47	0.359±0.028	99.68±0.35
2	**F2**	4.76±0.26	0.393±0.120	98.79±0.846
3	**F3**	5.1±0.235	0.326±0.132	98.49±0.446
4	**F4**	5.2±0.475	0.395±0.123	99.59±0.446
5	**F5**	5.0±0.365	0.333±0.065	99.59±0.386
6	**F6**	5.0±0.332	0.326±0.050	97.69±0.65
7	**F7**	5.9±0.345	0.34±0.01	98.19±0.356
8	**F8**	5.7±0.26	0.356±0.025	98.59±0.332
9	**F9**	5.1±0.248	0.396±0.075	99.16±0.326

n=3*

TABLE 9B-POSTCOMPRESSIONAL EVALUATION OF FEBUXOSTAT FLOATING SUSTAINED RELEASE MATRIX TABLET (NON-EFFERVESCENT TECHNIQUE)

S.no	Formulation code	Hardness Kg/cm^2	Friability (%) ± SD	Drug content (%)± SD
1	**G1**	5.16 ±0.34	0.369±0.035	97.84±0.332
2	**G2**	4.78±0.291	0.353±0.010	98.64±0.374
3	**G3**	5.12±0.224	0.386±0.135	98.68±0.398
4	**G4**	4.21±0.358	0.394±0.156	98.48±0.356
5	**G5**	4.03±0.578	0.359±0.0656	99.29±0.348
6	**G6**	4.63±0.621	0.369±0.050	99.89±0.62
7	**G7**	5.21±0.315	0.347±0.53	97.29±0.345
8	**G8**	5.36±0.231	0.368±0.053	97.59±0.33
9	**G9**	5.27 ±0.298	0.377±0.135	99.59±0.344

n=3*

TABLE 10A- *INVITRO* SWELLING INDEX OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (EFFERVESCENT TECHNIQUE)

S.NO	Formulation code	Percentage of swelling in time (hours) ± SD			
		3hrs	6hrs	9hrs	12hrs
1	**F1**	39.02 ± 1.5969	52.87 ± 0.2928	68.42 ±0.3894	76.91 ± 2.3081
2	**F2**	34.13 ± 1.5085	58.66 ± 1.7230	62.26 ±0.7823	78.51 ± 2.5517
3	**F3**	30.68 ± 1.931	56.79 ± 0.7552	69.42 ±0.7550	76.82 ± 1.0524
4	**F4**	34.35 ± 0.6908	54.87 ± 1.2206	64.34 ±1.3388	80.57 ± 1.0850
5	**F5**	38.06 ± 0.1789	55.44 ± 0.5645	62.66 ±0.5565	89.56 ± 1.2988
6	**F6**	38.57 ± 0.9500	56.12 ± 0.4712	60.71 ±0.4912	87.24 ± 1.0208
7	**F7**	37.78 ± 0.7937	57.73 ± 1.2833	63.11 ±1.2457	71.97 ± 1.1511
8	**F8**	39.00 ± 0.3750	52.56 ± 0.4467	66.62 ± 1.088	72.64 ± 0.84
9	**F9**	36.9 ± 0.6090	51.61± 1.1801	66.31 ±1.2234	70.50 ± 0.94384

n=3*

TABLE 10B- *INVITRO* SWELLING INDEX OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (NON- EFFERVESCENT TECHNIQUE)

S.NO	Formulation code	Percentage of swelling in time (hours) ± SD			
		3hrs	6hrs	9hrs	12hrs
1	**G1**	64.02 ± 1.59	69.87±0.2478	88.42 ±0.3964	70.35 ± 2.205
2	**G2**	59.04 ± 1.55	70.3 ± 1.6530	84.33 ±0.5823	73.51 ± 2.552
3	**G3**	56.21 ± 1.99	70.02±0.9852	89.66 ±0.5850	66.69 ± 1.084
4	**G4**	53.21 ± 0.65	64.7 ± 1.406	96.22 ±1.8988	75.23 ± 1.070
5	**G5**	57.3 ± 0.174	69.5 ± 0.5785	99.36 ± 0.565	72.23 ± 1.27
6	**G6**	54.7± 0.960	67.2 ± 0.4754	102.5 ± 0.452	70.24 ± 1.078
7	**G7**	59.78 ± 0.798	69.47±1.5833	86.52 ± 1.287	71.5 ± 1.121
8	**G8**	54.88 ± 0.3730	67.23±0.4487	88.85 ± 1.568	68.04 ± 0.841
9	**G9**	59.24± 0.609	61.85± 1.185	91.25 ± 1.284	74.25± 0.9584

n=3*

TABLE 11A -*INVITRO* BUOYANCY LAG TIME, TOTAL FLOATING TIME, SWELLING INDEX OF FLOATING SUSTAINED RELEASE TABLETS OF FEBUXOSTAT (EFFERVESCENT TECHNIQUE)

Formulation code	Buoyancy lag time (in minutes)	Total floating time (in hours)	Swelling index (%) (12hours)
F1	49 sec	>18	76.91 ± 2.3081
F2	52sec	>18	78.51 ± 2.5517
F3	48sec	>18	76.82 ± 1.0524
F4	23 sec	>18	80.57 ± 1.0850
F5	35sec	>18	89.56 ± 1.2988
F6	39sec	>18	87.24 ± 1.0208
F7	95sec	>18	71.97 ± 1.1511
F8	106sec	>18	72.64 ± 0.84
F9	89sec	>18	70.50 ± 0.94384

n=3*

TABLE 11B -*INVITRO* BUOYANCY LAG TIME, TOTAL FLOATING TIME, SWELLING INDEX OF FLOATING SUSTAINED RELEASE TABLETS OF FEBUXOSTAT (NON-EFFERVESCENT TECHNIQUE)

Formulation code	Buoyancy lag time (in minutes)	Total floating time (in hours)	Swelling index (%) (12 hours)
G1	302 sec	Not more than12	70.35 ± 2.205
G2	296 sec	Not more than12	73.51 ± 2.552
G3	305 sec	Not more than12	66.69 ± 1.084
G4	198sec	Not more than12	75.23 ± 1.070
G5	155sec	Not more than12	72.23 ± 1.27
G6	203sec	Not more than12	70.24 ± 1.078
G7	504sec	Not more than12	71.5± 1.121
G8	512sec	Not more than12	68.04 ± 0.841
G9	621sec	Not more than12	74.25± 0.9584

n=3*

TABLE 12 A- *IN VITRO* DRUG RELEASE PROFILE OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (EFFERVESCENT TECHNIQUE)

S.no	Time in hours	Formulation code Drug release in (%) ± SD		
		F1	F2	F3
1	1	26.9±0.45	29.3±0.18	27.9±0.58
2	2	32.7±0.33	34.6±0.32	31.8±0.68
3	3	36.9±0.07	38.8±0.17	35.8±0.47
4	4	41.9±0.36	41.8±0.32	39.2±0.77
5	5	44.7±0.58	44.3±0.08	42.6±0.42
6	6	48.03±0.37	46.7±0.36	44.9±0.32
7	7	52.6±0.14	52.5±0.17	50.8±0.39
8	8	62.6±0.98	57.9±1.89	54.6±0.6
9	9	66.7±0.35	62.3±0.35	58.7±0.78
10	10	67.8±0.77	65.4±0.65	63.2±0.77
11	11	71.9±0.96	70.6±0.17	68.8±1.99
12	12	75.3±0.17	74.6±0.45	73.6±1.79

n=3*

TABLE 12 A- *IN VITRO* DRUG RELEASE PROFILE OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (EFFERVESCENT TECHNIQUE)

S.no	Time in hours	Formulation code Drug release in (%) ± SD		
		F4	F5	F6
1	1	27.2±0.57	23.6±0.29	28.6±1.12
2	2	29.3±0.28	27.5±0.67	33.6±0.69
3	3	34.1±0.16	30.3±0.25	37.6±1.05
4	4	38.1±1.03	33.6±0.44	43.2±1.13
5	5	39.2±0.77	36.6±0.16	47.4±2.36
6	6	43.8±0.61	40.2±0.21	53.3±2.68
7	7	47.2±0.14	44.0±0.23	58.3±2.79
8	8	49.6±0.20	47.8±0.29	62.7±2.89
9	9	55.8±0.41	50.5±0.12	68.6±1.75
10	10	62.9±0.82	56.9±0.78	72.6±2.01
11	11	63.6±0.30	62.3±0.29	80.3±2.36
12	12	71.8±0.88	68.3±0.36	85.8±1.76

n=3*

TABLE 12 A- *IN VITRO* DRUG RELEASE PROFILE OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (EFFERVESCENT TECHNIQUE)

		Formulation code Drug release in (%) ± SD		
		F7	F8	F9
1	1	28.9±0.73	23.5±1.90	25.3±0.47
2	2	32.6±0.35	27.8±2.45	28.4±2.97
3	3	36.5±0.47	32.6±3.30	33.4±3.23
4	4	43.2±0.56	36.8±3.47	35.9±3.26
5	5	47.1±0.26	38.9±3.31	40.7±4.00
6	6	52.5±0.84	43.8±3.21	44.5±3.63
7	7	57.5±1.15	49.3±3.16	51.2±3.63
8	8	63.9±1.21	58.2±3.77	53.9±4.51
9	9	69.5±0.96	60.9±3.72	60.2±4.46
10	10	74.4±0.30	69.3±2.90	65.5±3.66
11	11	79.6±0.56	75.5±2.35	73.1±3.28
12	12	81.2±0.21	83.7±2.36	82.0±2.78

n=3*

TABLE 12 B- *IN VITRO* DRUG RELEASE PROFILE OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (NON-EFFERVESCENT TECHNIQUE)

S.no	Time in hours	Formulation code Drug release in (%) ± SD		
		G1	G2	G3
1	1	27.2±0.87	25.3±0.57	27.0±0.28
2	2	31.6±1.12	29.5±0.36	33.4±0.20
3	3	34.8±1.18	33.2±1.51	37.5±0.40
4	4	40.8±1.06	40.2±0.58	42.8±0.53
5	5	45.5±1.69	44.8±0.36	45.8±0.28
6	6	50.9±2.12	51.8±0.45	47.8±0.24
7	7	55.9±2.68	55.7±0.59	52.4±0.69
8	8	64.2±1.74	59.4±1.92	59.6±1.06
9	9	72.6±1.10	65.5±1.63	63.7±1.39
10	10	74.2±1.12	70.8±2.14	68.2±1.84
11	11	79.2±1.12	73.4±2.17	73.6±0.60
12	12	85.2±0.39	89.6±0.78	92.6±0.58

n=3*

TABLE 12 B- *IN VITRO* DRUG RELEASE PROFILE OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (NON- EFFERVESCENT TECHNIQUE)

S.no	Time in hours	Formulation code Drug release in (%) ± SD		
		G4	G5	G6
1	1	24.6±0.29	27.2±0.63	27.9±0.28
2	2	28.0±0.98	33.8±1.00	33.9±0.47
3	3	31.5±1.04	39.2±0.54	40.5±0.16
4	4	37.8±0.97	44.5±0.67	44.9±2.40
5	5	42.8±0.66	46.9±0.23	49.3±1.66
6	6	47.8±0.45	51.5±0.63	56.4±1.48
7	7	51.6±0.16	57.5±0.49	62.9±1.14
8	8	56.9±0.60	62.9±0.17	71.8±1.38
9	9	62.8±0.39	68.8±0.50	76.8±1.58
10	10	67.8±0.7	75.2±0.49	80.9±0.75
11	11	72.8±0.59	83.9±0.87	84.9±1.11
12	12	77.7±0.30	90.9±0.65	89.7±0.36

n=3*

TABLE 12 B- *IN VITRO* DRUG RELEASE PROFILE OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (NON- EFFERVESCENT TECHNIQUE)

S.no	Time in hours	Formulation code Drug release in (%) ± SD		
		G7	G8	G9
1	1	25.9±1.52	26.8±0.20	24.3±1.31
2	2	30.8±1.18	32.8±0.38	28.6±2.15
3	3	36.7±1.60	38.9±0.28	33.6±2.28
4	4	42.8±1.79	41.8±0.29	38.9±2.15
5	5	48.1±3.08	47.5±0.74	43.9±1.87
6	6	55.6±2.00	55.6±0.42	47.5±2.53
7	7	61.2±3.69	61.5±0.20	54.2±2.36
8	8	67.8±2.28	67.9±0.37	59.9±2.69
9	9	72.8±1.98	72.5±0.26	65.8±2.56
10	10	76.5±0.86	76.8±0.22	72.8±2.36
11	11	84.8±0.53	80.6±0.48	78.9±2.04
12	12	88.2±0.69	87.5±0.37	86.8±1.39

n=3*

TABLE 13A- *IN VITRO* SUSTAINED DISSOLUTION STUDIES OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (EFFERVESCENT TECHNIQUE)

S.no	Time in hours	Formulation code	Drug release in (%) ± SD 12 hours
1	1	**F1**	75.3±0.17
2	2	**F2**	74.6±0.45
3	3	**F3**	73.6±1.79
4	4	**F4**	71.8±0.88
5	5	**F5**	68.3±0.36
6	6	**F6**	75.8±1.76
7	7	**F7**	81.2±0.21
8	8	**F8**	83.7±2.36
9	9	**F9**	82.0±2.78

n=3*

TABLE 13B- *IN VITRO* SUSTAINED DISSOLUTION STUDIES OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (NON-EFFERVESCENT TECHNIQUE)

S.*no*	Time in hours	Formulation code	Drug release in (%) ± SD 12 hours
1	1	**G1**	85.2±0.39
2	2	**G2**	89.6±0.78
3	3	**G3**	92.6±0.58
4	4	**G4**	77.7±0.30
5	5	**G5**	90.9±0.65
6	6	**G6**	81.7±0.36
7	7	**G7**	88.2±0.69
8	8	**G8**	87.5±0.37
9	9	**G9**	86.8±1.39

n=3*

TABLE14A- *IN VITRO* KINETIC RELEASE STUDY DATA FOR FEBUXOSTAT SUATAINED RELEASE FLOATING TABLETS(EFFERVESCENT)

FORMULATION CODE	ZERO ORDER		FIRST ORDER		HIGHUCHI MODEL		KORES-MEYER AND PEPPAS MODEL		HIXON-CROWELL MODEL	
	r^2	$k^0(h^{-1})$	r^2	k_1 (h^{-1})	r^2	$k_h(h^{-1/2})$	r^2	n	r^2	$K_{HC}(h^{-1/3})$
F1	0.9179	5.2004	0.9829	-4.4586	0.9795	20.818	0.9534	0.3987	0.9769	-0.1163
F2	0.9813	4.5932	0.9625	-3.7942	0.9463	18.399	0.8886	0.3542	0.929	-0.0971
F3	0.9133	4.7536	0.9946	-4.0732	0.9751	19.206	0.936	0.3852	0.9758	-0.1028
F4	0.9071	4.5592	0.9819	-3.8363	0.9635	18.155	0.9136	0.3852	0.9576	-0.0942
F5	0.9338	4.5373	0.9841	-3.9502	0.9623	17.795	0.926	0.4316	0.9575	-0.0931
F6	0.9424	5.8657	0.9963	-5.1206	0.9814	23.124	0.9577	0.4586	0.9664	-0.147
F7	0.9381	5.7661	0.9971	-5.0027	0.9852	22.831	0.9581	0.4521	0.9861	-0.1404
F8	0.9489	5.5259	0.9758	-4.9617	0.9472	21.332	0.9534	0.4307	0.9214	-0.1316
F9	0.9608	5.8384	0.9819	-5.321	0.9493	22.422	0.9282	0.5126	0.9389	-0.143

FORMULATION CODE	ZERO ORDER		FIRST ORDER		HIGHUCHI MODEL		KORES-MEYER AND PEPPAS MODEL		HIXON-CROWELL MODEL	
	r^2	$k^0(h^{-1})$	r^2	k_1 (h^{-1})	r^2	$k_h(h^{-1/2})$	r^2	n	r^2	$K_{HC}(h^{-1/3})$
G1	0.9557	6.1134	0.991	-5.4692	0.9684	23.777	0.9356	0.4884	0.9632	-0.1567
G2	0.9532	5.9907	0.9799	-5.3972	0.9591	23.218	0.9382	0.5034	0.8966	-0.1546
G3	0.9196	5.703	0.9497	-5.002	0.9394	22.27	0.9197	0.4412	0.8184	-0.1504
G4	0.9573	5.5089	0.9977	-4.9112	0.9767	21.499	0.9478	0.4899	0.9805	-0.1268
G5	0.9475	6.1288	0.9892	-5.4229	0.969	23.946	0.9527	0.4726	0.9252	-0.1649
G6	0.952	6.5045	0.994	-5.7703	0.9826	25.532	0.9604	0.4945	0.9808	-0.1787
G7	0.9659	6.5323	0.9981	-5.9023	0.9806	25.431	0.9659	0.5336	0.9752	-0.1768
G8	0.9523	6.2293	0.9945	-5.5267	0.9836	24.46	0.9654	0.498	0.9786	-0.162
G9	0.9654	6.0796	0.9907	-5.5323	0.9587	23.408	0.9405	0.5136	0.9419	-0.1551

TABLE 15A- EVALUATION OF FEBUXOSTAT FLOATING TABLETS KEPT IN STABILITY AT 40^{O}C/75RH RELATIVE HUMIDITY

Formulation Parameters	Initial	15 days	30days	45days	60days
Average weight (mg)	346.73	346.73	346.72	346.72	346.72
Thickness (mg)	4.26	4.26	4.26	4.26	4.26
Hardness (kg/cm^2)	10.3	10.3	10.3	10.3	10.3
Floating lag Time(sec)	35sec	39sec	32sec	42 sec	40sec
Swelling Index (8 Hours) (%)	89.56	88.02	87.18	87.03	86.09
Drug content in %	99.59±0.38	99.59±0.34	99.23±0.28	99.21±0.20	98.04±0.18
% drug release at 12hrs	68.3±0.36	-----	------	----	63.3±0.28

n=3*

TABLE 1: CALIBRATION OF FEBUXOSTAT BY USING ACID BUFFER OF Ph1.2

CONCENTRATION	ABSORBANCE
2	0.058±0.010
4	0.121±0.016
6	0.179±0.022
8	0.238±0.031
10	0.301±0.045
12	0.353±0.051
14	0.411±0.048
16	0.469±0.060
18	0.528±0.058
20	0.601±0.062

n=3* **Regression Value – 0.99976**

TABLE 2: COMPOSITION OF SOLID DISPERSION

S.NO	Formulation code	Method	Ratio	Composition
1	A1	Melting	1:1	Drug : PEG6000
2	A2	Melting	1:2	Drug : PEG6000
3	A3	Melting	1:3	Drug : PEG6000

TABLE 3 : PERCENTAGE YIELD AND DRUG CONTENT OF SOLID DISPERSION

S.no	Formulation Code	Method	Ratio	Percentage of yield ± SD	Drug content ± SD
1	A1	Melting	1 : 1	87.09±0.01	95.38 ± 0.20
2	A2	Melting	1 : 2	88.21±0.16	96.61 ± 0.07
3	A3	Melting	1 : 3	94.75±0.03	98.55 ± 0.80

n=3*

TABLE 4: CUMULATIVE PERCENTAGE OF DRUG RELEASE OF PHYSICAL MIXTURE OF FEBUXOSTAT WITH PEG6000.

Time (min)	Percentage of drug release ± SD				
	A1 1 :1	A2 1 :2	A3 1:3	MARKETED FORMULATION	PURE DRUG
10	11.9 ±1.87	22.4 ±1.95	31.2 ± 2.08	13.6±2.55	9.16±2.97
20	19.5± 2.47	31.8 ±2.71	38.5 ± 3.05	24.5±0.007	19.25 ±0.95
30	29.1 ±1.18	39.5 ± 3.05	47.2 ± 2.78	29.5±1.25	29.34±3.06
40	34.2 ±1.08	43.2 ± 2.49	54.9± 2.3	33.8±1.28	36.71 ±1.75
50	41.4 ±1.54	51.9 ± 1.52	61.8 ± 2.54	46.4±2.57	42.4 ±3.27
60	44.5 ±2.48	59.4 ± 2.24	67.2 ± 2.78	53.6±3.08	49.1 ±1.70

n=3*

TABLE 4: CUMULATIVE PERCENTAGE OF DRUG RELEASE OF FEBUXOSTAT WITH PEG6000 AFTER SOLID DISPERSION BY MELTING METHOD

Time (min)	Percentage of drug release ± SD				
	A1 1 :1	A2 1 : 2	A3 1:3	MARKETED FORMULATION	PURE DRUG
10	26.7 ±1.66	31.1 ± 2.42	42.9±1.25	13.6±2.55	9.16±2.97
20	33.7 ±3.36	39.2 ± 1.40	50.6 ± 1.42	24.5±0.007	19.25 ±0.95
30	43.7 ±2.70	46.2 ± 1.63	64.4±3.39	29.5±1.25	29.34±3.06
40	47.9 ±2.04	51.4 ± 2.08	74.8 ± 4.05	33.8±1.28	36.71 ±1.75
50	54.1 ±2.37	58.8 ± 2.97	86.9 ± 3.15	46.4±2.57	42.4 ±3.27
60	59.4 ±2.50	66.7 ± 3.37	92.9 ± 1.82	53.6±3.08	27.1 ±1.70

n=3*

TABLE 6A:FORMULATION OF EFFERVESCENT FLOATING SUSTAINED RELEASE MATRIX TABLET

Quantity (mg) for I tablet (Average weight -350mg)

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
SOLID DISPERSION IN 1:3 RATIO (mg) [CONTAINING 40 MG FEBUXOSTAT]	160	160	160	160	160	160	160	160	160
HPMC K4M (mg)	35	70	105						
HPMC K100M (mg)				35	70	105			
METHYL CELLULOSE (mg)							35	70	105
PVP K30 (mg)	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5
SODIUM BICARBONATE (mg)	35	35	35	35	35	35	35	35	35
CITRIC ACID (mg)	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5
MCC (mg)	78	43	8	78	43	8	73	43	8
MAGNESIUM STEARATE (mg)	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
TALC (mg)	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
TOTAL WEIGHT OF EACH TABLET (mg)	350	350	350	350	350	350	350	350	350

TABLE 6B--FORMULATION OF NON- EFFERVESCENT FLOATING SUSTAINED RELEASE MATRIX TABLETS

Average Weight 200mg / Tablet

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
SOLID DISPERSION IN 1:3 RATIO (mg) [CONTAINING 40 MG FEBUXOSTAT]	160	160	160	160	160	160	160	160	160
HPMC K4M (mg)	70	105	140						
HPMC K100M (mg)				70	105	140			
METHYL CELLULOSE (mg)							70	105	140
ETHYL CELLULOSE (mg)	35	35	35	35	35	35	35	35	35
MCC (mg)	78	43	8	78	43	8	78	43	8
MAGNESIUM STEARATE (mg)	3.5	3.5	3.5	3.5	3.5	3.5	35	3.5	3.5
TALC (mg)	3.5	3.5	3.5	3.	3.5	3.5	3.5	3.5	3.5
TOTAL WEIGHT OF EACH TABLET (mg)	350	350	350	350	350	350	350	350	350

TABLE 7A- PRECOMPRESSIONAL EVALUATION OF POWDER BLEND (EFFERVESCENT TECHNIQUE)

S.no	Formulation code	Angle of repose ± SD	Bulk density (gm/ml)± SD	Tapped density (g/ml) ± SD
1	**F1**	28 ^{0}47' ± 0.5	0.736± 0.01	0.84 ± 0.02
2	**F2**	29^{0}19' ± 0.49	0.777 ±0.01	0.87 ± 0.011
3	**F3**	25^{0}84' ± 0.65	0.80 ± 0.02	0.91 ± 0.035
4	**F4**	30^{0}57' ± 1.56	0.764 ± 0.02	0.84 ± 0.02
5	**F5**	31^{0}09' ± 1.87	0.721 ± 0.03	0.87± 0.023
6	**F6**	29^{0}34' ± 0.98	0.827± 0.01	0.94 ± 0.034
7	**F7**	31^{0}10' ± 0.51	0.914 ± 0.01	1.03 ± 0.02
8	**F8**	25^{0}58' ± 1.55	0.775 ± 0.02	0.89 ± 0.02
9	**F9**	28^{0}72' ± 1.35	0.784 ± 0.03	0.94 ± 0.025

n=3*

TABLE 7B- PRECOMPRESSIONAL EVALUATION OF POWDER BLEND (NON-EFFERVESCENT TECHNIQUE)

S.no	Formulation code	Angle of repose ± SD	Bulk density (gm/ml)± SD	Tapped density (g/ml) ± SD
1	**G1**	27 ^{0}08' ± 0.5	0.747 ± 0.01	0.87 ± 0.02
2	**G2**	29^{0}53' ± 0.49	0.754 ± 0.01	0.88 ± 0.011
3	**G3**	28^{0}24' ± 0.65	0.674 ± 0.02	0.78 ± 0.035
4	**G4**	29^{0}54' ± 1.56	0.725 ± 0.02	0.86 ± 0.02
5	**G5**	30^{0}26' ± 1.87	0.871 ± 0.03	1.08± 0.023
6	**G6**	28^{0}50' ± 0.98	0.768± 0.01	0.94 ± 0.034
7	**G7**	28^{0}34' ± 0.51	0.684 ± 0.01	0.76 ± 0.02
8	**G8**	28^{0}35' ± 1.55	0.789 ± 0.02	0.95± 0.02
9	**G9**	28^{0}24' ± 1.35	0.725 ± 0.03	0.88 ± 0.025

n=3*

TABLE 8A- PRECOMPRESSIONAL EVALUATION OF POWDER BLEND (EFFERVESCENT TECHNIQUE)

S.no	Formulation Code	Compressibility index(%) ±SD	Hausners ratio (HR)±SD
1	**F1**	13.09 ± 2.74	1.15 ± 0.03
2	**F2**	11.49 ± 0.24	1.12 ± 0.31
3	**F3**	12.08 ± 1.55	1.13 ± 0.05
4	**F4**	13.69± 2.09	1.10 ± 0.03
5	**F5**	17.24 ± 2.23	1.20± 0.05
6	**F6**	12.76 ± 0.15	1.14 ± 0.01
7	**F7**	11.26 ± 1.08	1.13 ± 0.01
8	**F8**	13.48 ± 1.96	1.15 ± 0.32
9	**F9**	17.02 ± 0.52	1.20 ± 0.14

n=3*

TABLE 8B- PRECOMPRESSIONAL EVALUATION OF POWDER BLEND (NON-EFFERVESCENT TECHNIQUE)

S.no	Formulation code	Compressibility index(%) ±SD	Hausners ratio (HR)±SD
1	**G1**	14.94 ± 0.32	1.17 ± 0.05
2	**G2**	14.77 ± 0.15	1.17 ± 0.33
3	**G3**	14.10± 1.41	1.16 ± 0.02
4	**G4**	16.27 ± 2.06	1.19 ± 0.03
5	**G5**	19.44 ± 2.03	1.24 ± 0.05
6	**G6**	19.14 ± 0.14	1.23 ± 0.05
7	**G7**	10.52 ± 1.02	1.11 ± 0.09
8	**G8**	17.89 ± 1.45	1.21 ± 0.32
9	**G9**	18.18 ± 0.23	1.22 ± 0.04

n=3*

TABLE 9A-POSTCOMPRESSIONAL EVALUATION OF FEBUXOSTAT FLOATING SUSTAINED RELEASE MATRIX TABLET (EFFERVESCENT TECHNIQUE)

S.no	Formulation code	Hardness Kg/cm^2	Friability (%) ± SD	Drug content (%)± SD
1	**F1**	4.26 ±0.47	0.359±0.028	99.68±0.35
2	**F2**	4.76±0.26	0.393±0.120	98.79±0.846
3	**F3**	5.1±0.235	0.326±0.132	98.49±0.446
4	**F4**	5.2±0.475	0.395±0.123	99.59±0.446
5	**F5**	5.0±0.365	0.333±0.065	99.59±0.386
6	**F6**	5.0±0.332	0.326±0.050	97.69±0.65
7	**F7**	5.9±0.345	0.34±0.01	98.19±0.356
8	**F8**	5.7±0.26	0.356±0.025	98.59±0.332
9	**F9**	5.1±0.248	0.396±0.075	99.16±0.326

n=3*

TABLE 9B-POSTCOMPRESSIONAL EVALUATION OF FEBUXOSTAT FLOATING SUSTAINED RELEASE MATRIX TABLET (NON-EFFERVESCENT TECHNIQUE)

S.no	Formulation code	Hardness Kg/cm^2	Friability (%) ± SD	Drug content (%)± SD
1	**G1**	5.16 ±0.34	0.369±0.035	97.84±0.332
2	**G2**	4.78±0.291	0.353±0.010	98.64±0.374
3	**G3**	5.12±0.224	0.386±0.135	98.68±0.398
4	**G4**	4.21±0.358	0.394±0.156	98.48±0.356
5	**G5**	4.03±0.578	0.359±0.0656	99.29±0.348
6	**G6**	4.63±0.621	0.369±0.050	99.89±0.62
7	**G7**	5.21±0.315	0.347±0.53	97.29±0.345
8	**G8**	5.36±0.231	0.368±0.053	97.59±0.33
9	**G9**	5.27 ±0.298	0.377±0.135	99.59±0.344

n=3*

TABLE 10A- *INVITRO* SWELLING INDEX OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (EFFERVESCENT TECHNIQUE)

S.NO	Formulation code	Percentage of swelling in time (hours) ± SD			
		3hrs	6hrs	9hrs	12hrs
1	**F1**	39.02 ± 1.5969	52.87 ± 0.2928	68.42 ±0.3894	76.91 ± 2.3081
2	**F2**	34.13 ± 1.5085	58.66 ± 1.7230	62.26 ±0.7823	78.51 ± 2.5517
3	**F3**	30.68 ± 1.931	56.79 ± 0.7552	69.42 ±0.7550	76.82 ± 1.0524
4	**F4**	34.35 ± 0.6908	54.87 ± 1.2206	64.34 ±1.3388	80.57 ± 1.0850
5	**F5**	38.06 ± 0.1789	55.44 ± 0.5645	62.66 ±0.5565	89.56 ± 1.2988
6	**F6**	38.57 ± 0.9500	56.12 ± 0.4712	60.71 ±0.4912	87.24 ± 1.0208
7	**F7**	37.78 ± 0.7937	57.73 ± 1.2833	63.11 ±1.2457	71.97 ± 1.1511
8	**F8**	39.00 ± 0.3750	52.56 ± 0.4467	66.62 ± 1.088	72.64 ± 0.84
9	**F9**	36.9 ± 0.6090	51.61± 1.1801	66.31 ±1.2234	70.50 ± 0.94384

n=3*

TABLE 10B- *INVITRO* SWELLING INDEX OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (NON- EFFERVESCENT TECHNIQUE)

S.NO	Formulation code	Percentage of swelling in time (hours) ± SD			
		3hrs	6hrs	9hrs	12hrs
1	**G1**	64.02 ± 1.59	69.87±0.2478	88.42 ±0.3964	70.35 ± 2.205
2	**G2**	59.04 ± 1.55	70.3 ± 1.6530	84.33 ±0.5823	73.51 ± 2.552
3	**G3**	56.21 ± 1.99	70.02±0.9852	89.66 ±0.5850	66.69 ± 1.084
4	**G4**	53.21 ± 0.65	64.7 ± 1.406	96.22 ±1.8988	75.23 ± 1.070
5	**G5**	57.3 ± 0.174	69.5 ± 0.5785	99.36 ± 0.565	72.23 ± 1.27
6	**G6**	54.7± 0.960	67.2 ± 0.4754	102.5 ± 0.452	70.24 ± 1.078
7	**G7**	59.78 ± 0.798	69.47±1.5833	86.52 ± 1.287	71.5 ± 1.121
8	**G8**	54.88 ± 0.3730	67.23±0.4487	88.85 ± 1.568	68.04 ± 0.841
9	**G9**	59.24± 0.609	61.85± 1.185	91.25 ± 1.284	74.25± 0.9584

n=3*

TABLE 11A -*INVITRO* BUOYANCY LAG TIME, TOTAL FLOATING TIME, SWELLING INDEX OF FLOATING SUSTAINED RELEASE TABLETS OF FEBUXOSTAT (EFFERVESCENT TECHNIQUE)

Formulation code	Buoyancy lag time (in minutes)	Total floating time (in hours)	Swelling index (%) (12hours)
F1	49 sec	>18	76.91 ± 2.3081
F2	52sec	>18	78.51 ± 2.5517
F3	48sec	>18	76.82 ± 1.0524
F4	23 sec	>18	80.57 ± 1.0850
F5	35sec	>18	89.56 ± 1.2988
F6	39sec	>18	87.24 ± 1.0208
F7	95sec	>18	71.97 ± 1.1511
F8	106sec	>18	72.64 ± 0.84
F9	89sec	>18	70.50 ± 0.94384

n=3*

TABLE 11B -*INVITRO* BUOYANCY LAG TIME, TOTAL FLOATING TIME, SWELLING INDEX OF FLOATING SUSTAINED RELEASE TABLETS OF FEBUXOSTAT (NON-EFFERVESCENT TECHNIQUE)

Formulation code	Buoyancy lag time (in minutes)	Total floating time (in hours)	Swelling index (%) (12 hours)
G1	302 sec	Not more than12	70.35 ± 2.205
G2	296 sec	Not more than12	73.51 ± 2.552
G3	305 sec	Not more than12	66.69 ± 1.084
G4	198sec	Not more than12	75.23 ± 1.070
G5	155sec	Not more than12	72.23 ± 1.27
G6	203sec	Not more than12	70.24 ± 1.078
G7	504sec	Not more than12	71.5± 1.121
G8	512sec	Not more than12	68.04 ± 0.841
G9	621sec	Not more than12	74.25± 0.9584

n=3*

TABLE 12 A- *IN VITRO* DRUG RELEASE PROFILE OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (EFFERVESCENT TECHNIQUE)

S.no	Time in hours	Formulation code Drug release in (%) ± SD		
		F1	F2	F3
1	1	26.9±0.45	29.3±0.18	27.9±0.58
2	2	32.7±0.33	34.6±0.32	31.8±0.68
3	3	36.9±0.07	38.8±0.17	35.8±0.47
4	4	41.9±0.36	41.8±0.32	39.2±0.77
5	5	44.7±0.58	44.3±0.08	42.6±0.42
6	6	48.03±0.37	46.7±0.36	44.9±0.32
7	7	52.6±0.14	52.5±0.17	50.8±0.39
8	8	62.6±0.98	57.9±1.89	54.6±0.6
9	9	66.7±0.35	62.3±0.35	58.7±0.78
10	10	67.8±0.77	65.4±0.65	63.2±0.77
11	11	71.9±0.96	70.6±0.17	68.8±1.99
12	12	75.3±0.17	74.6±0.45	73.6±1.79

n=3*

TABLE 12 A- *IN VITRO* DRUG RELEASE PROFILE OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (EFFERVESCENT TECHNIQUE)

S.no	Time in hours	Formulation code Drug release in (%) ± SD		
		F4	F5	F6
1	1	27.2±0.57	23.6±0.29	28.6±1.12
2	2	29.3±0.28	27.5±0.67	33.6±0.69
3	3	34.1±0.16	30.3±0.25	37.6±1.05
4	4	38.1±1.03	33.6±0.44	43.2±1.13
5	5	39.2±0.77	36.6±0.16	47.4±2.36
6	6	43.8±0.61	40.2±0.21	53.3±2.68
7	7	47.2±0.14	44.0±0.23	58.3±2.79
8	8	49.6±0.20	47.8±0.29	62.7±2.89
9	9	55.8±0.41	50.5±0.12	68.6±1.75
10	10	62.9±0.82	56.9±0.78	72.6±2.01
11	11	63.6±0.30	62.3±0.29	80.3±2.36
12	12	71.8±0.88	68.3±0.36	85.8±1.76

n=3*

TABLE 12 A- *IN VITRO* DRUG RELEASE PROFILE OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (EFFERVESCENT TECHNIQUE)

		Formulation code Drug release in (%) ± SD		
		F7	F8	F9
1	1	28.9±0.73	23.5±1.90	25.3±0.47
2	2	32.6±0.35	27.8±2.45	28.4±2.97
3	3	36.5±0.47	32.6±3.30	33.4±3.23
4	4	43.2±0.56	36.8±3.47	35.9±3.26
5	5	47.1±0.26	38.9±3.31	40.7±4.00
6	6	52.5±0.84	43.8±3.21	44.5±3.63
7	7	57.5±1.15	49.3±3.16	51.2±3.63
8	8	63.9±1.21	58.2±3.77	53.9±4.51
9	9	69.5±0.96	60.9±3.72	60.2±4.46
10	10	74.4±0.30	69.3±2.90	65.5±3.66
11	11	79.6±0.56	75.5±2.35	73.1±3.28
12	12	81.2±0.21	83.7±2.36	82.0±2.78

n=3*

TABLE 12 B- *IN VITRO* DRUG RELEASE PROFILE OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (NON-EFFERVESCENT TECHNIQUE)

S.no	Time in hours	Formulation code Drug release in (%) ± SD		
		G1	G2	G3
1	1	27.2±0.87	25.3±0.57	27.0±0.28
2	2	31.6±1.12	29.5±0.36	33.4±0.20
3	3	34.8±1.18	33.2±1.51	37.5±0.40
4	4	40.8±1.06	40.2±0.58	42.8±0.53
5	5	45.5±1.69	44.8±0.36	45.8±0.28
6	6	50.9±2.12	51.8±0.45	47.8±0.24
7	7	55.9±2.68	55.7±0.59	52.4±0.69
8	8	64.2±1.74	59.4±1.92	59.6±1.06
9	9	72.6±1.10	65.5±1.63	63.7±1.39
10	10	74.2±1.12	70.8±2.14	68.2±1.84
11	11	79.2±1.12	73.4±2.17	73.6±0.60
12	12	85.2±0.39	89.6±0.78	92.6±0.58

n=3*

TABLE 12 B- *IN VITRO* DRUG RELEASE PROFILE OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (NON- EFFERVESCENT TECHNIQUE)

S.no	Time in hours	Formulation code Drug release in (%) ± SD		
		G4	G5	G6
1	1	24.6±0.29	27.2±0.63	27.9±0.28
2	2	28.0±0.98	33.8±1.00	33.9±0.47
3	3	31.5±1.04	39.2±0.54	40.5±0.16
4	4	37.8±0.97	44.5±0.67	44.9±2.40
5	5	42.8±0.66	46.9±0.23	49.3±1.66
6	6	47.8±0.45	51.5±0.63	56.4±1.48
7	7	51.6±0.16	57.5±0.49	62.9±1.14
8	8	56.9±0.60	62.9±0.17	71.8±1.38
9	9	62.8±0.39	68.8±0.50	76.8±1.58
10	10	67.8±0.7	75.2±0.49	80.9±0.75
11	11	72.8±0.59	83.9±0.87	84.9±1.11
12	12	77.7±0.30	90.9±0.65	89.7±0.36

n=3*

TABLE 12 B- *IN VITRO* DRUG RELEASE PROFILE OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (NON- EFFERVESCENT TECHNIQUE)

S.no	Time in hours	Formulation code Drug release in (%) ± SD		
		G7	G8	G9
1	1	25.9±1.52	26.8±0.20	24.3±1.31
2	2	30.8±1.18	32.8±0.38	28.6±2.15
3	3	36.7±1.60	38.9±0.28	33.6±2.28
4	4	42.8±1.79	41.8±0.29	38.9±2.15
5	5	48.1±3.08	47.5±0.74	43.9±1.87
6	6	55.6±2.00	55.6±0.42	47.5±2.53
7	7	61.2±3.69	61.5±0.20	54.2±2.36
8	8	67.8±2.28	67.9±0.37	59.9±2.69
9	9	72.8±1.98	72.5±0.26	65.8±2.56
10	10	76.5±0.86	76.8±0.22	72.8±2.36
11	11	84.8±0.53	80.6±0.48	78.9±2.04
12	12	88.2±0.69	87.5±0.37	86.8±1.39

n=3*

TABLE 13A- *IN VITRO* SUSTAINED DISSOLUTION STUDIES OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (EFFERVESCENT TECHNIQUE)

S.no	Time in hours	Formulation code	Drug release in (%) ± SD 12 hours
1	1	**F1**	75.3±0.17
2	2	**F2**	74.6±0.45
3	3	**F3**	73.6±1.79
4	4	**F4**	71.8±0.88
5	5	**F5**	68.3±0.36
6	6	**F6**	75.8±1.76
7	7	**F7**	81.2±0.21
8	8	**F8**	83.7±2.36
9	9	**F9**	82.0±2.78

n=3*

TABLE 13B- *IN VITRO* SUSTAINED DISSOLUTION STUDIES OF FLOATING SUSTAINED RELEASE MATRIX TABLETS OF FEBUXOSTAT (NON-EFFERVESCENT TECHNIQUE)

S.*no*	Time in hours	Formulation code	Drug release in (%) ± SD 12 hours
1	1	**G1**	85.2±0.39
2	2	**G2**	89.6±0.78
3	3	**G3**	92.6±0.58
4	4	**G4**	77.7±0.30
5	5	**G5**	90.9±0.65
6	6	**G6**	81.7±0.36
7	7	**G7**	88.2±0.69
8	8	**G8**	87.5±0.37
9	9	**G9**	86.8±1.39

n=3*

TABLE14A- *IN VITRO* KINETIC RELEASE STUDY DATA FOR FEBUXOSTAT SUATAINED RELEASE FLOATING TABLETS(EFFERVESCENT)

FORMULATION CODE	ZERO ORDER		FIRST ORDER		HIGHUCHI MODEL		KORES-MEYER AND PEPPAS MODEL		HIXON-CROWELL MODEL	
	r^2	$k^0(h^{-1})$	r^2	k_1 (h^{-1})	r^2	$k_h(h^{-1/2})$	r^2	n	r^2	$K_{HC}(h^{-1/3})$
F1	0.9179	5.2004	0.9829	-4.4586	0.9795	20.818	0.9534	0.3987	0.9769	-0.1163
F2	0.9813	4.5932	0.9625	-3.7942	0.9463	18.399	0.8886	0.3542	0.929	-0.0971
F3	0.9133	4.7536	0.9946	-4.0732	0.9751	19.206	0.936	0.3852	0.9758	-0.1028
F4	0.9071	4.5592	0.9819	-3.8363	0.9635	18.155	0.9136	0.3852	0.9576	-0.0942
F5	0.9338	4.5373	0.9841	-3.9502	0.9623	17.795	0.926	0.4316	0.9575	-0.0931
F6	0.9424	5.8657	0.9963	-5.1206	0.9814	23.124	0.9577	0.4586	0.9664	-0.147
F7	0.9381	5.7661	0.9971	-5.0027	0.9852	22.831	0.9581	0.4521	0.9861	-0.1404
F8	0.9489	5.5259	0.9758	-4.9617	0.9472	21.332	0.9534	0.4307	0.9214	-0.1316
F9	0.9608	5.8384	0.9819	-5.321	0.9493	22.422	0.9282	0.5126	0.9389	-0.143

FORMULATION CODE	ZERO ORDER		FIRST ORDER		HIGHUCHI MODEL		KORES-MEYER AND PEPPAS MODEL		HIXON-CROWELL MODEL	
	r^2	$k^0(h^{-1})$	r^2	k_1 (h^{-1})	r^2	$k_h(h^{-1/2})$	r^2	n	r^2	$K_{HC}(h^{-1/3})$
G1	0.9557	6.1134	0.991	-5.4692	0.9684	23.777	0.9356	0.4884	0.9632	-0.1567
G2	0.9532	5.9907	0.9799	-5.3972	0.9591	23.218	0.9382	0.5034	0.8966	-0.1546
G3	0.9196	5.703	0.9497	-5.002	0.9394	22.27	0.9197	0.4412	0.8184	-0.1504
G4	0.9573	5.5089	0.9977	-4.9112	0.9767	21.499	0.9478	0.4899	0.9805	-0.1268
G5	0.9475	6.1288	0.9892	-5.4229	0.969	23.946	0.9527	0.4726	0.9252	-0.1649
G6	0.952	6.5045	0.994	-5.7703	0.9826	25.532	0.9604	0.4945	0.9808	-0.1787
G7	0.9659	6.5323	0.9981	-5.9023	0.9806	25.431	0.9659	0.5336	0.9752	-0.1768
G8	0.9523	6.2293	0.9945	-5.5267	0.9836	24.46	0.9654	0.498	0.9786	-0.162
G9	0.9654	6.0796	0.9907	-5.5323	0.9587	23.408	0.9405	0.5136	0.9419	-0.1551

TABLE 15A- EVALUATION OF FEBUXOSTAT FLOATING TABLETS KEPT IN STABILITY AT 40^{O}C/75RH RELATIVE HUMIDITY

Formulation Parameters	Initial	15 days	30days	45days	60days
Average weight (mg)	346.73	346.73	346.72	346.72	346.72
Thickness (mg)	4.26	4.26	4.26	4.26	4.26
Hardness (kg/cm^2)	10.3	10.3	10.3	10.3	10.3
Floating lag Time(sec)	35sec	39sec	32sec	42 sec	40sec
Swelling Index (8 Hours) (%)	89.56	88.02	87.18	87.03	86.09
Drug content in %	99.59±0.38	99.59±0.34	99.23±0.28	99.21±0.20	98.04±0.18
% drug release at 12hrs	68.3±0.36	-----	------	----	63.3±0.28

n=3*

FIG.1 DETERMINATION OF λ max OF FEBUXOSTAT IN ACID BUFFER pH 1.2

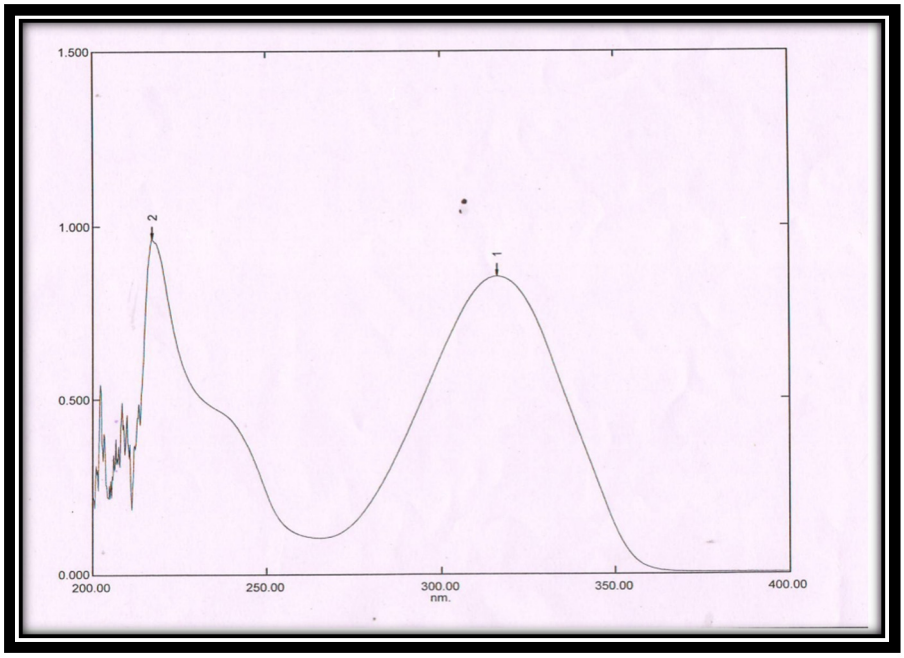


FIG.2 CALIBRATION OF FEBUXOSTAT USING ACID BUFFER pH 1.2

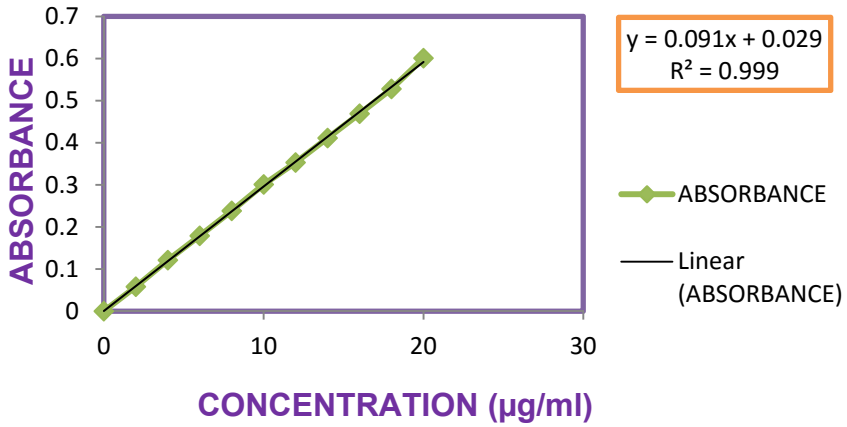


FIG.3A-1 FTIR STUDY OF FEBUXOSTAT

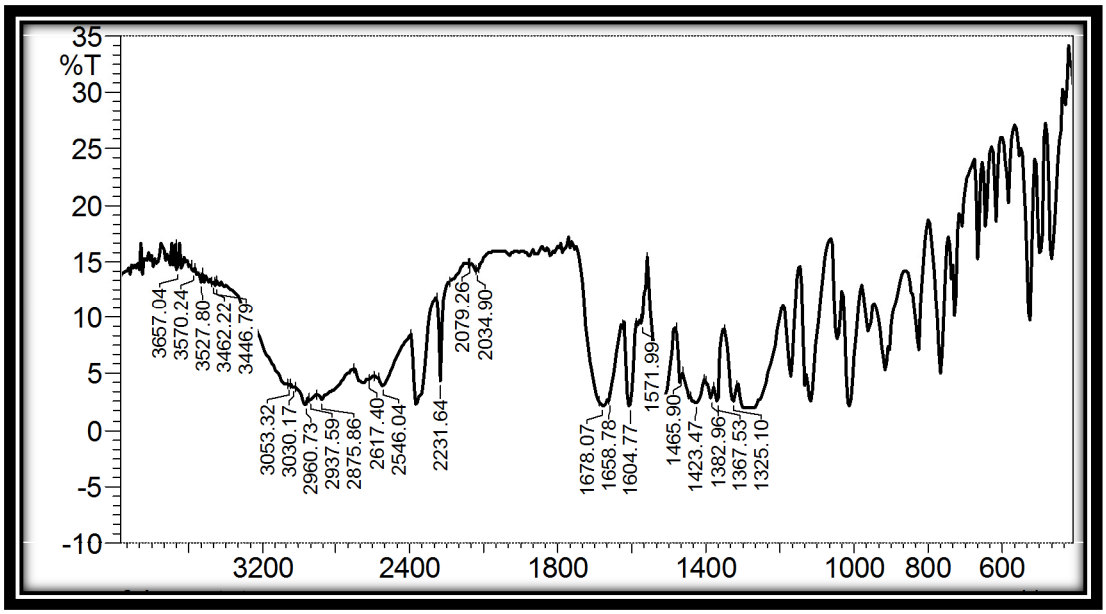


FIG.3A-2 FTIR STUDY OF FEBUXOSTAT AND PEG 6000 (1:3) SOLID DISPERSION

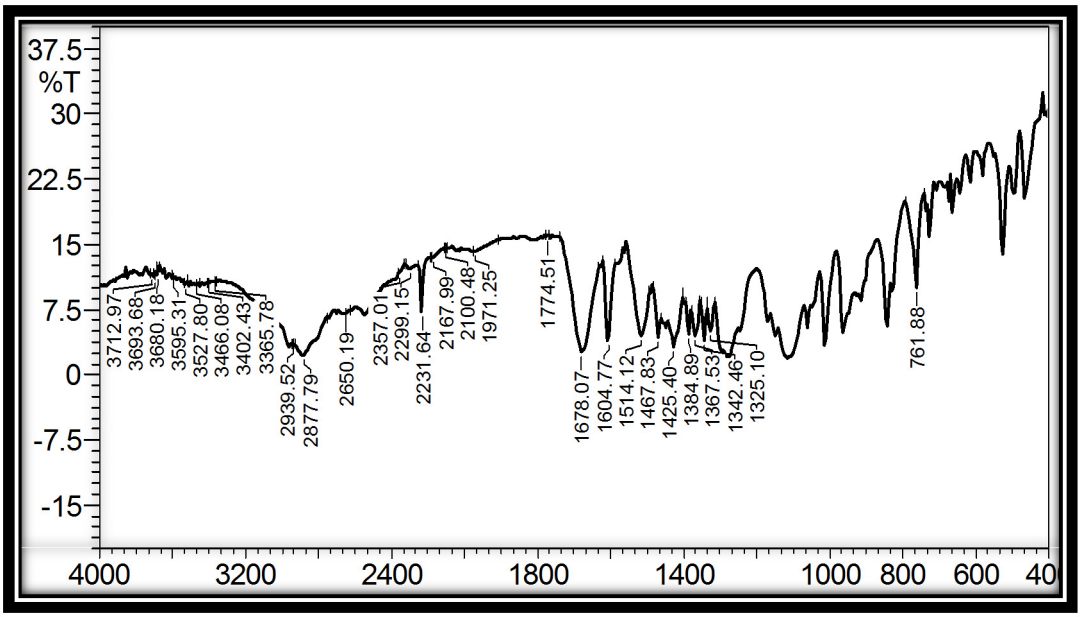


FIG.3A-3 FTIR STUDY OF FEBUXOSTAT WITH HPMCK4M

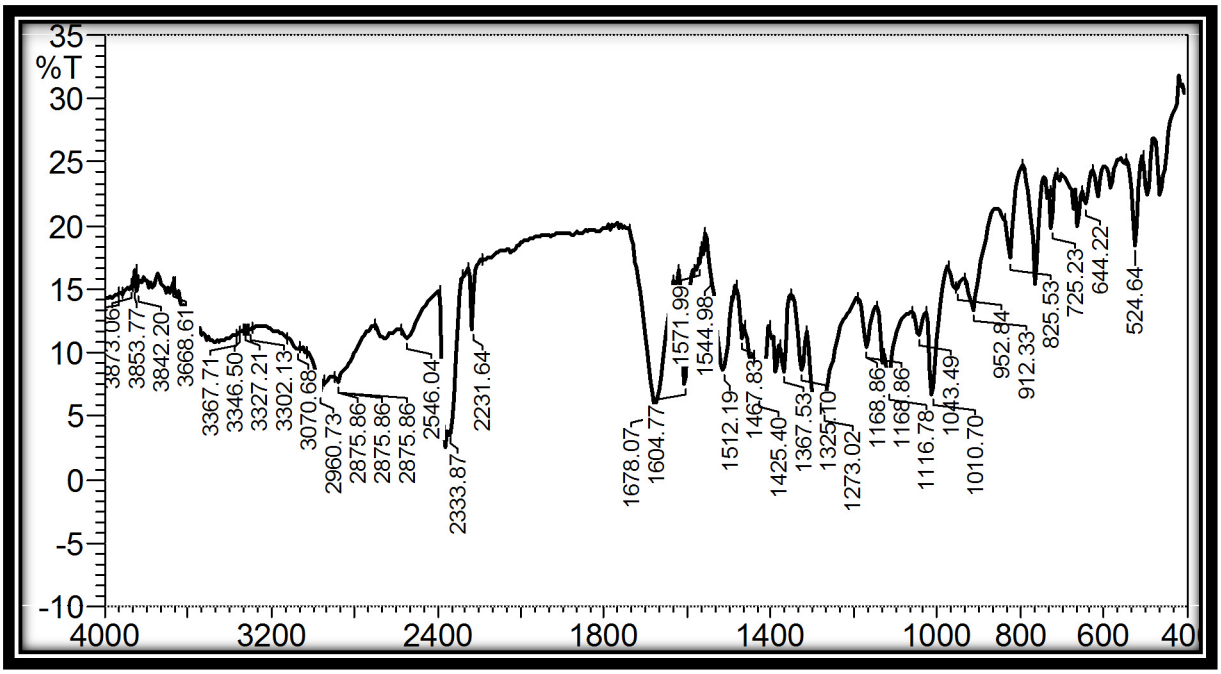


FIG.3A-4 FTIR STUDY OF FEBUXOSTAT WITH HPMC K100M

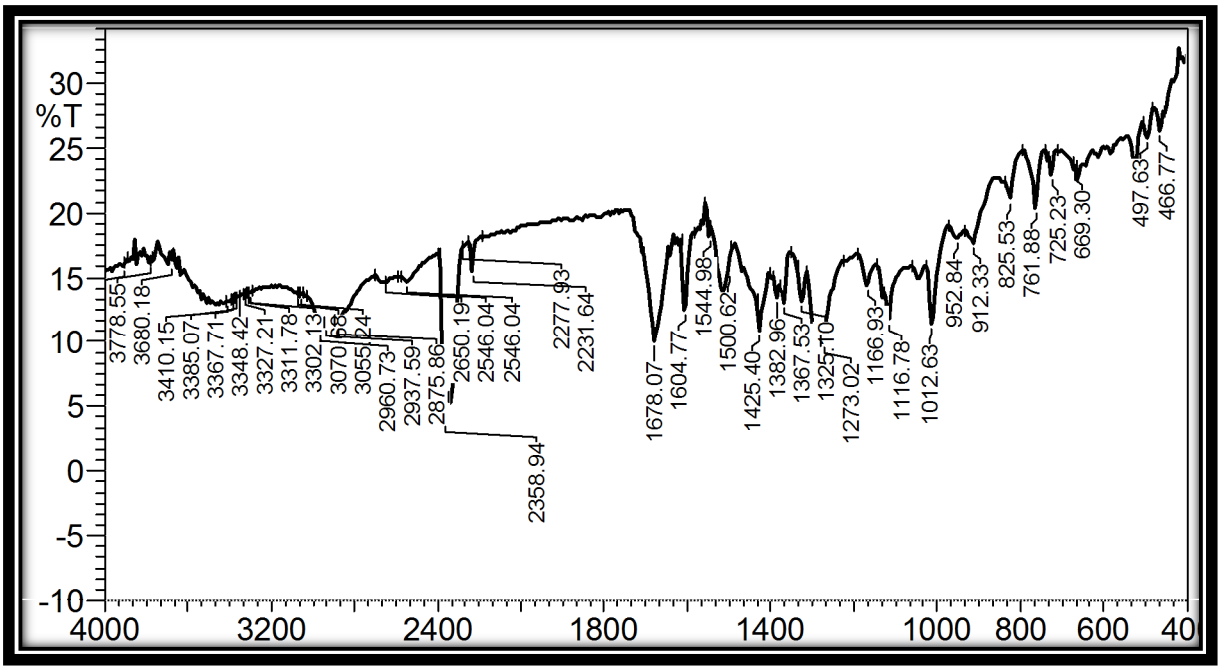


FIG.3A-5 FTIR STUDY OF FEBUXOSTAT WITH METHYL CELLULOSE

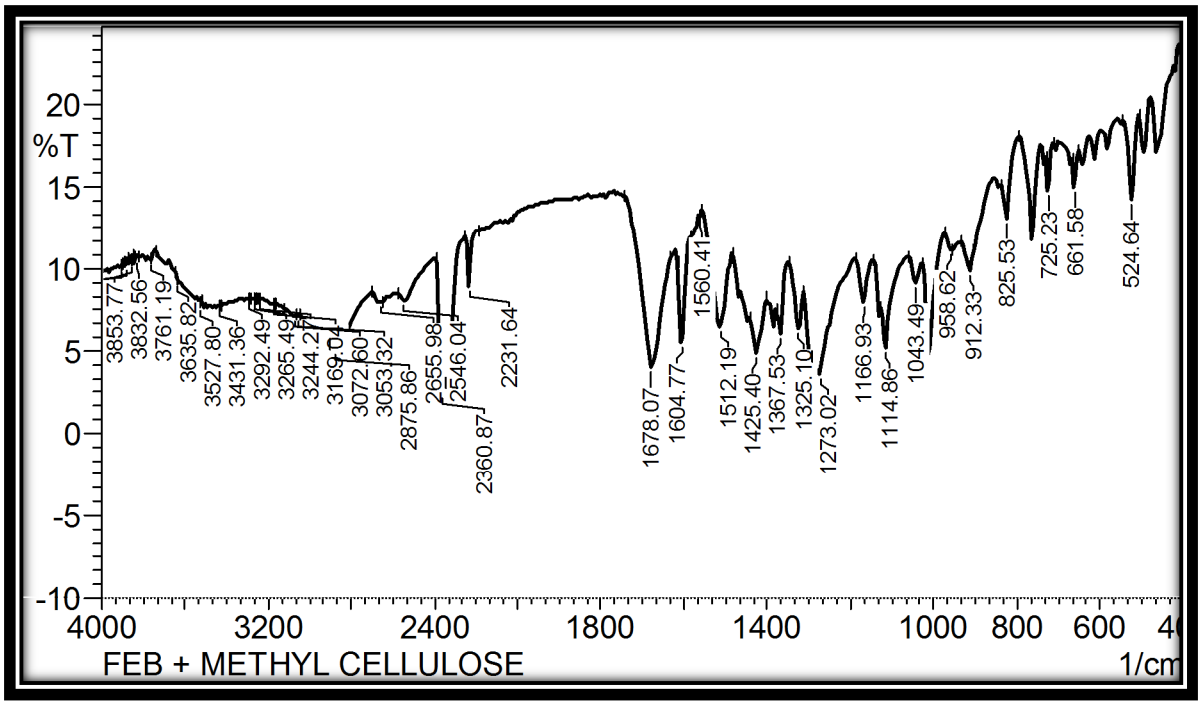


FIG.3A-6 FTIR STUDY OF FEBUXOSTAT WITH ETHYL CELLULOSE

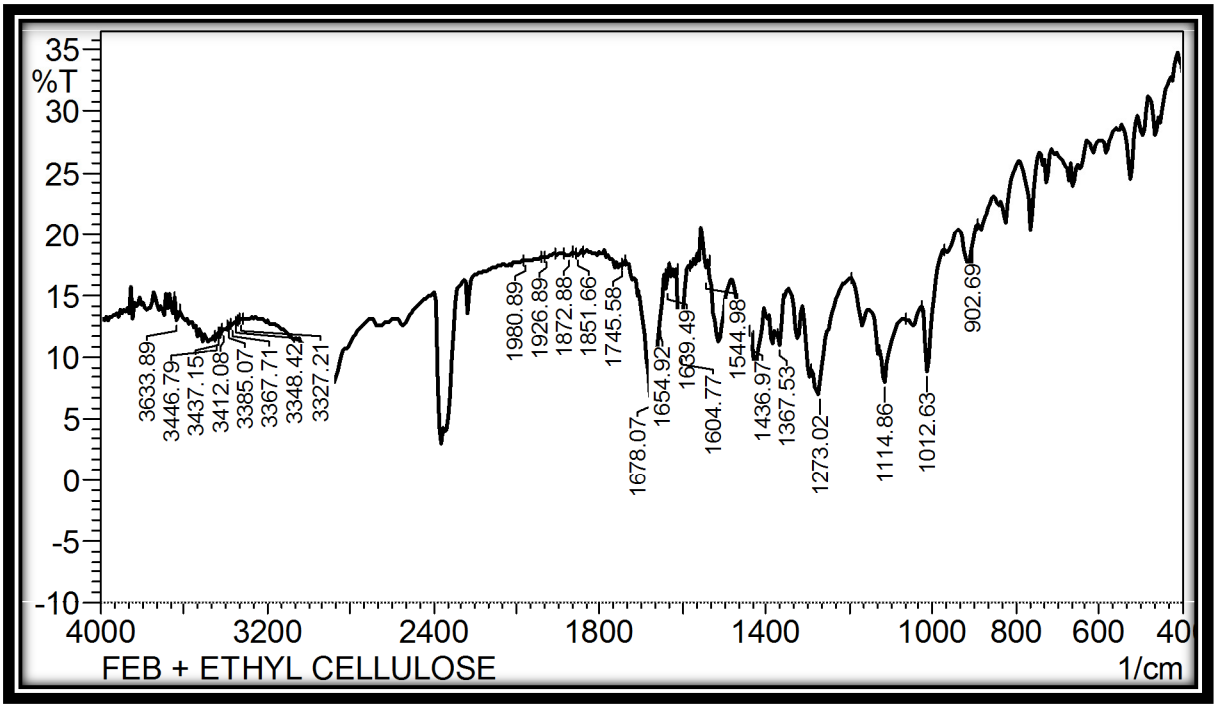


FIG.3C FTIR STUDY OF FEBUXOSTAT + PEG6000+HPMCK4+ HPMC K 100+ METHYLCELLULOSE+PVPK30+SODIUM BICARBONATE+CITRIC ACID+MCC+TALC+MAGNESIUM STEARATE

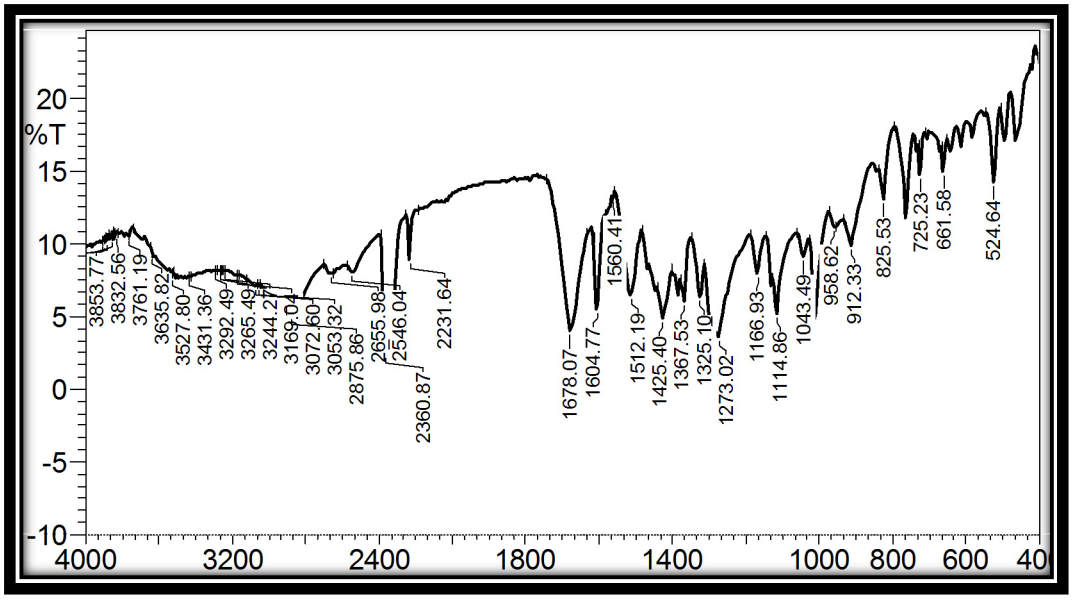


FIG.3D FTIR STUDY OF FEBUXOSTAT + PEG6000+HPMCK4+ HPMC K 100+ METHYLCELLULOSE+ETHYL CELLULOSE+MCC+TALC+MAGNESIUM STEARATE

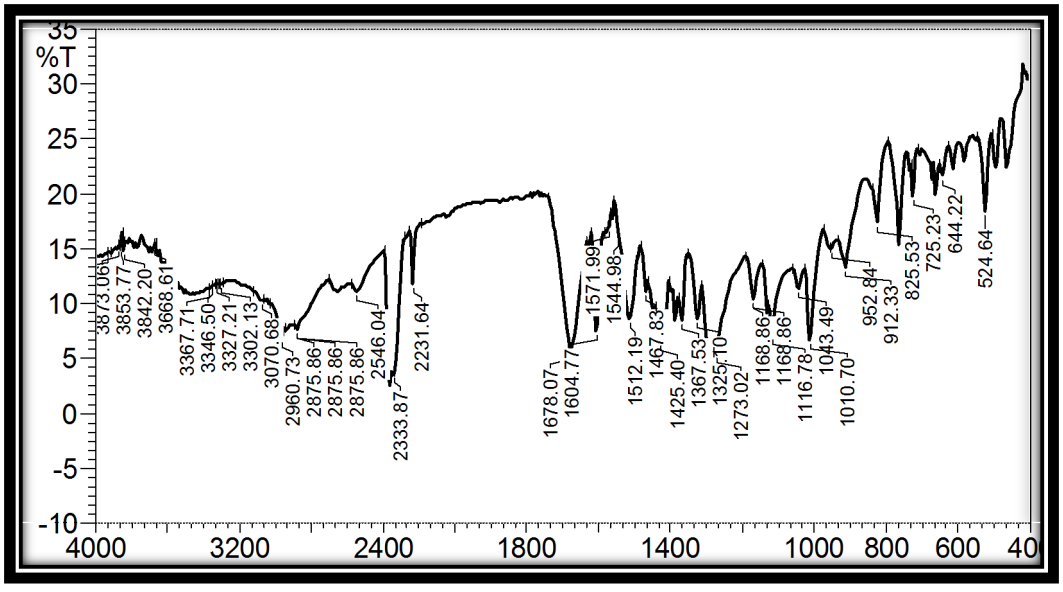


FIGURE 4A: DSC THERMOGRAM OF FEBUXOSTAT PURE DRUG

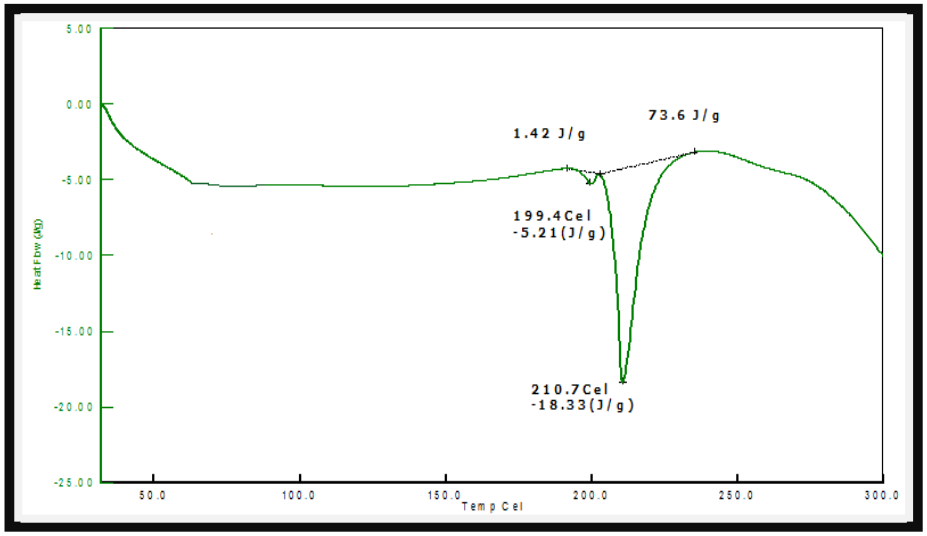


FIGURE 4B: DSC THERMOGRAM OF FEBUXOSTAT WITH PEG6000 SOLID DISPERSION (1:3)

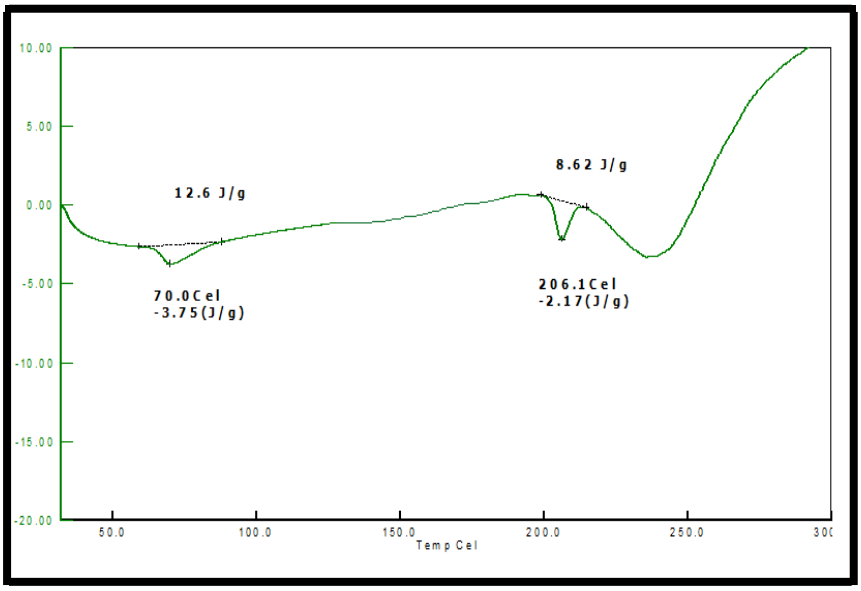


FIGURE 5A: PXRD PATTERN OF FEBUXOSTAT PURE DRUG

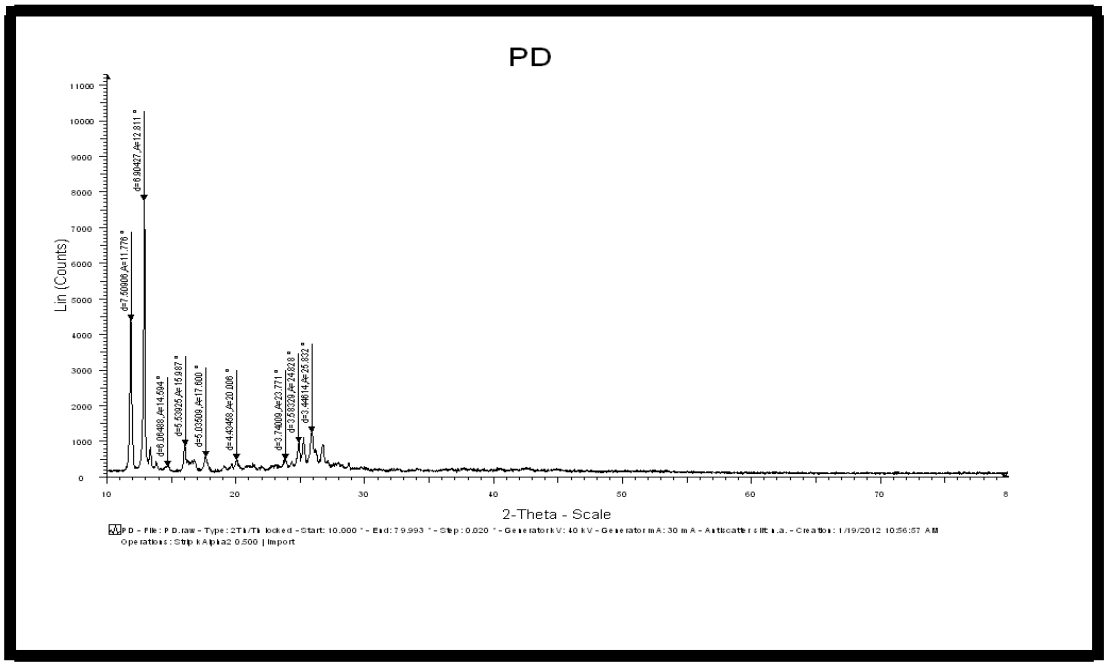


FIGURE 5B: PXRD PATTERN OF FEBUXOSTAT AND PEG6000(1:3)

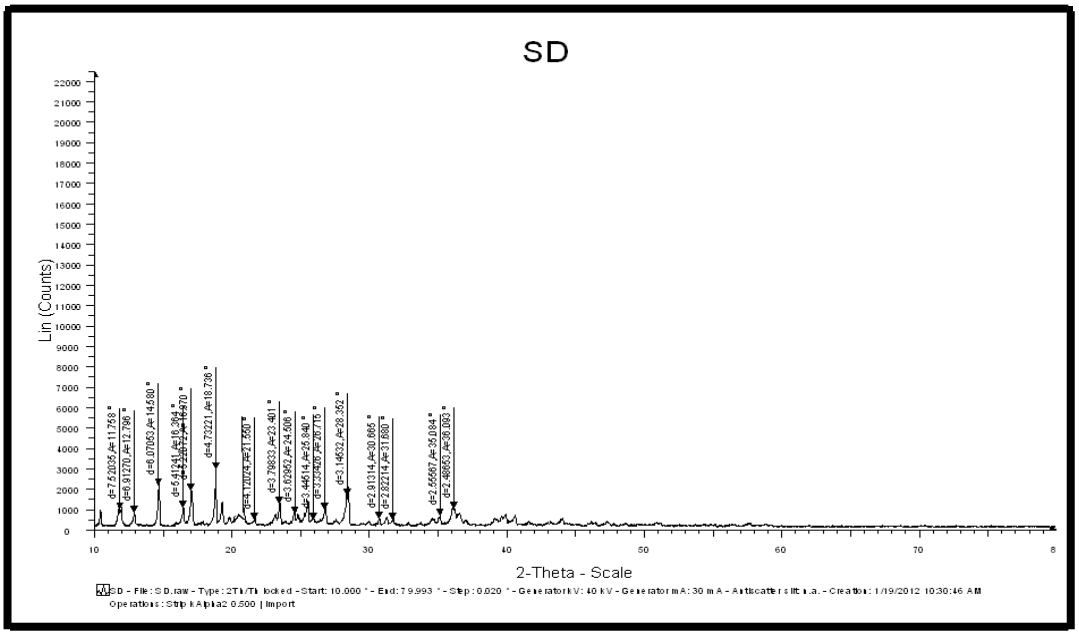


FIGURE 6A- PERCENTAGE YIELD AND DRUG CONTENT OF FEBUXOSTAT SOLID FISPERSION WITH PEG6000

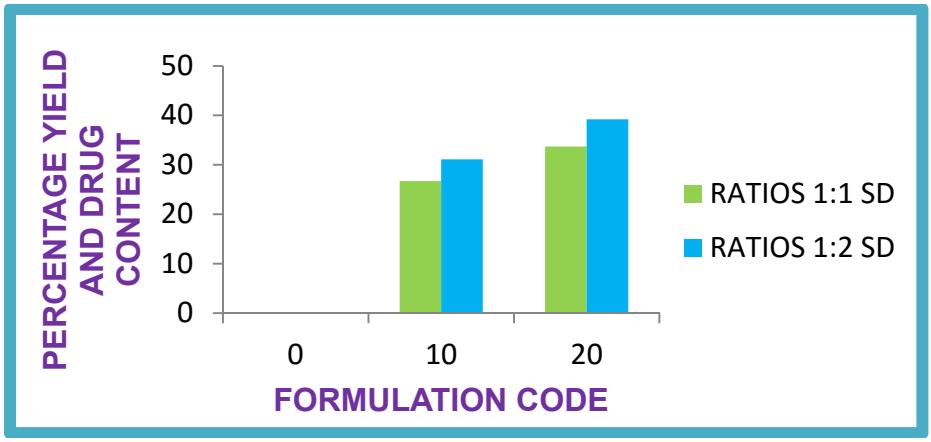


FIGURE 6B: CUMULATIVE PERCENTAGE DRUG RELEASE OF PHYSICAL MIXTURE OF FEBUXOSTAT WIH PEG6000

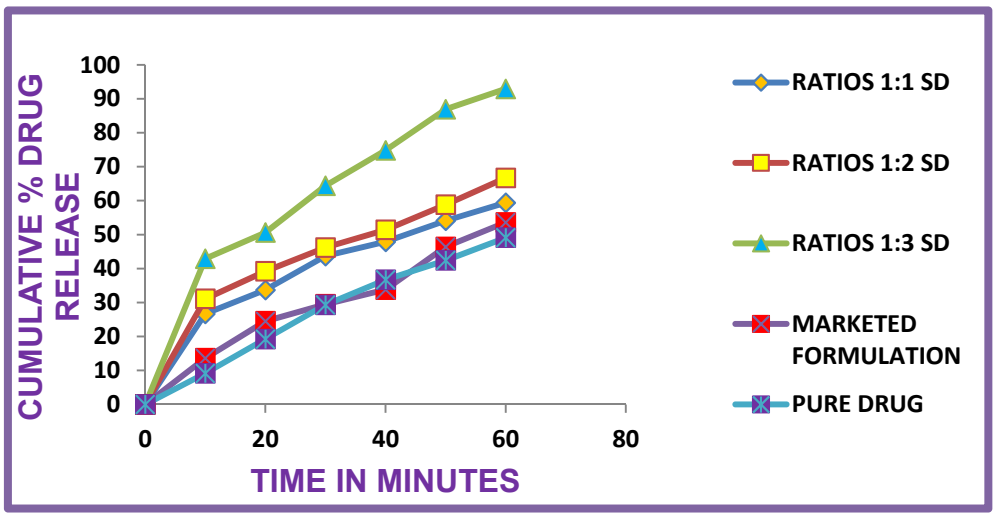


FIGURE 6C: CUMULATIVE PERCENTAGE DRUG RELEASE OF SOLID DISPERSION OF FEBUXOSTAT WIH PEG6000

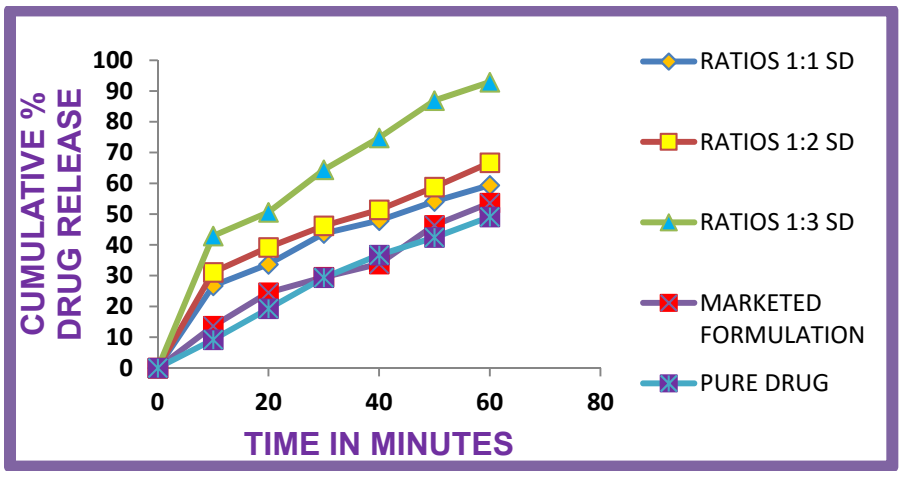


FIGURE 7A: COMPARITIVE ANGLE OF REPOSE FOR FORMULATIONS (F1-F9) AND (G1-G9)

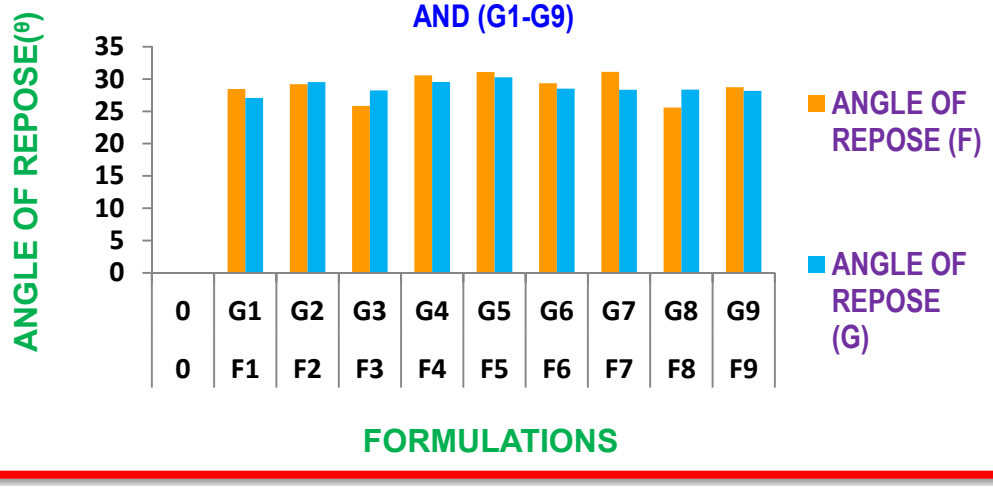


FIGURE 7B: COMPARITIVE BULK DENSITY FOR FORMULATIONS (F1-F9) AND (G1-G9)

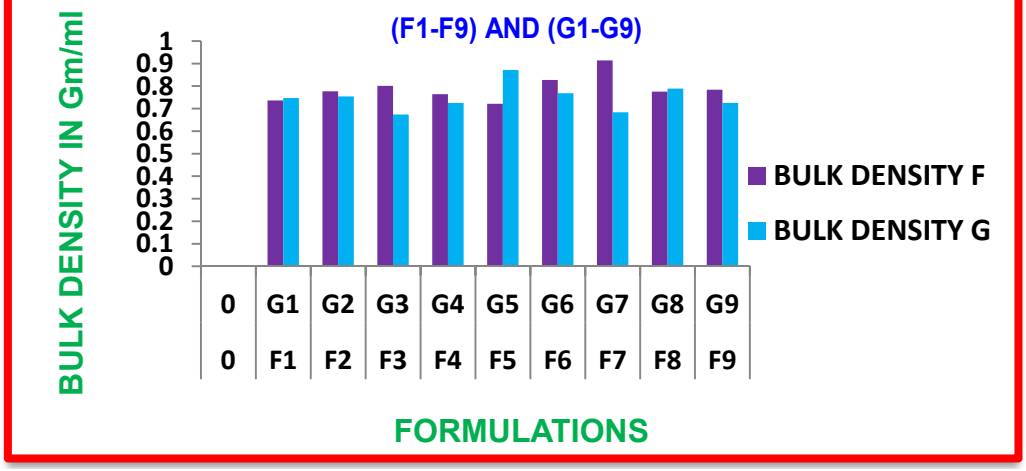


FIGURE 7C: COMPARITIVE TAPPED DENSITY FOR FORMULATIONS (F1-F9) AND (G1-G9)

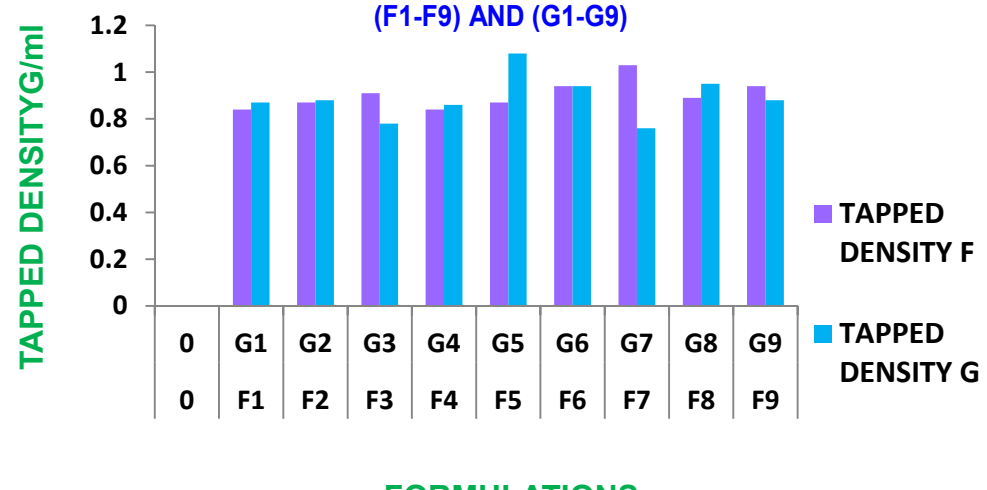


FIGURE 7D: COMPARITIVE COMPRESSIBILITY INDEX FOR FORMULATIONS (F1-F9) AND (G1-G9)

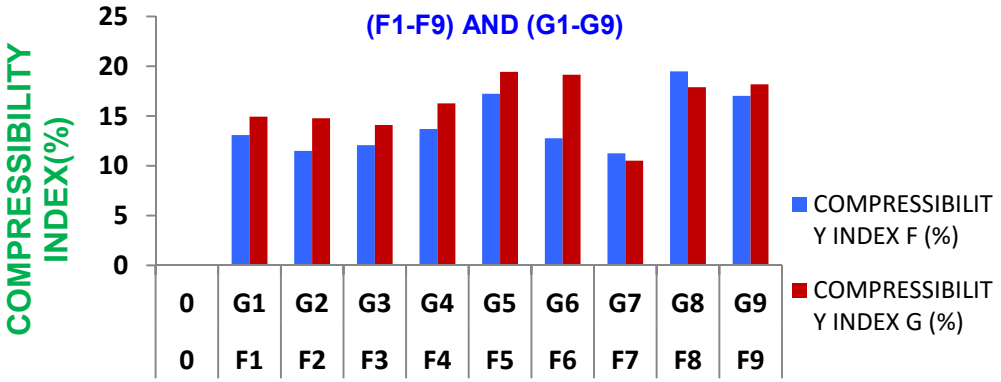


FIGURE 7E: COMPARITIVE HAUSNERS RATIO FOR FORMULATIONS (F1-F9) AND (G1-G9)

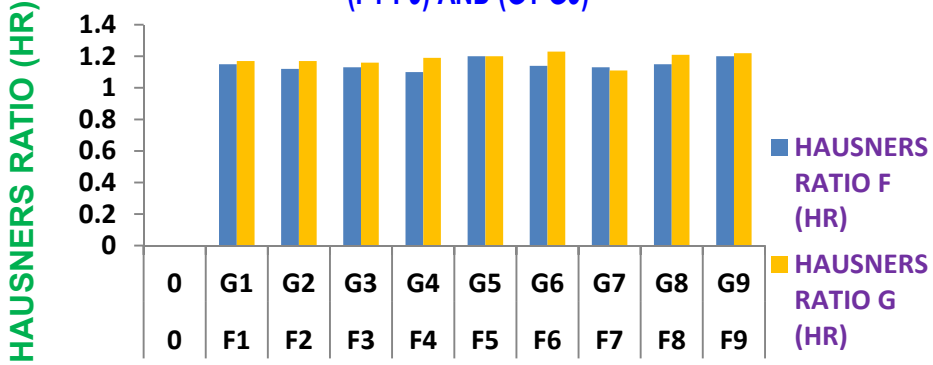


FIGURE 7F: COMPARITIVE DRUG CONTENT FOR FORMULATIONS (F1-F9) AND (G1-G9)

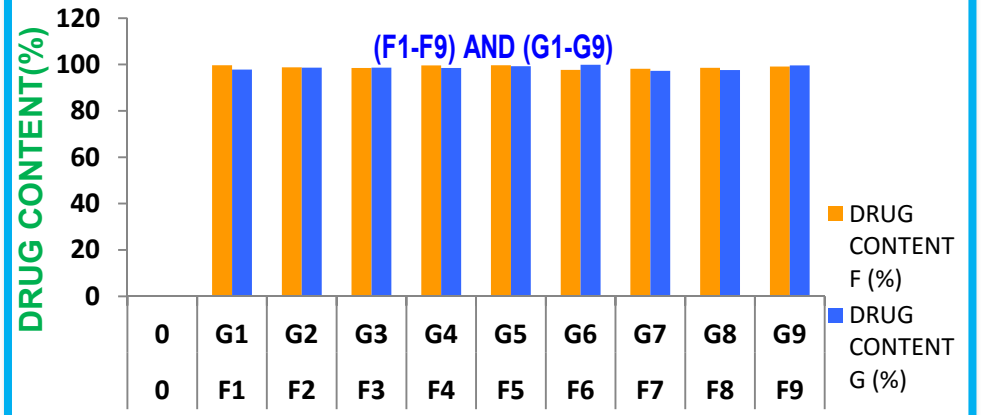


TABLE 7G: COMPARITIVE SWELLING INDEX FOR FORMULATIONS (F1-F9) AND (G1-G9)

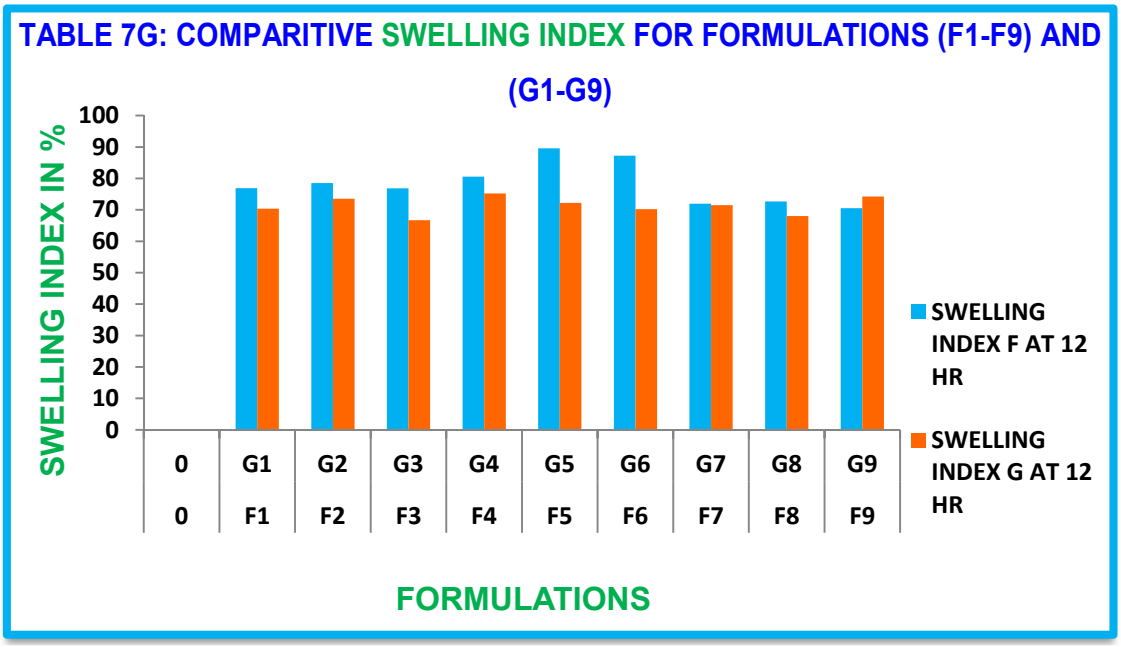


FIGURE 8A *IN-VITRO* BUOYANCY STUDIES OF FLOATING TABLET OF FEBUXOSTAT EFERVESCENT FORMULATION (BEST) F5

AT 0 SECOND

AT 34TH SECOND

AFTER 35TH SECOND

FIGURE 8B *IN-VITRO* SWELLING INDEX STUDIES OF FLOATING TABLET OF FEBUXOSTAT EFERVESCENT FORMULATION (BEST) F5

FIGURE 9A *IN* VITRO DRUG RELEASE PROFILE OF FEBUXOSTAT AND HPMC K4M (F1-F3) AT DIFFERENT CONCENTRATIONS

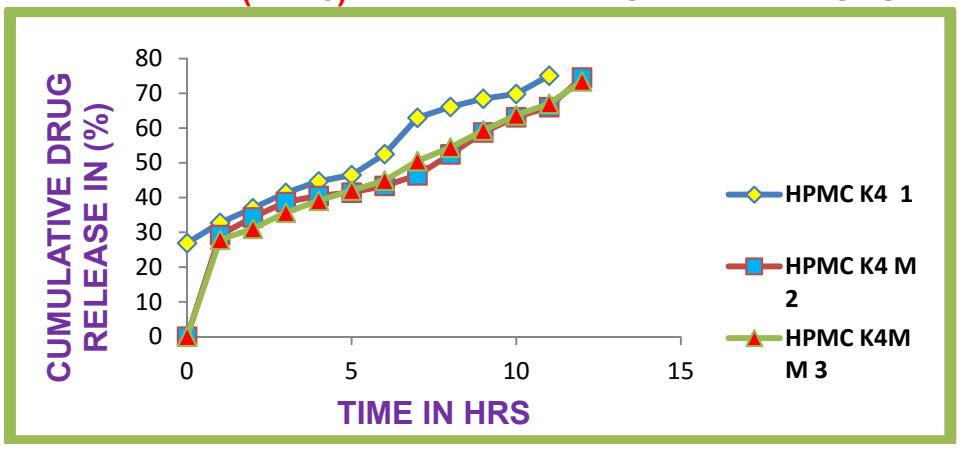


FIGURE 9B *IN* VITRO DRUG RELEASE PROFILE OF FEBUXOSTAT AND HPMC K100M (F4-F6) AT DIFFERENT CONCENTRATIONS

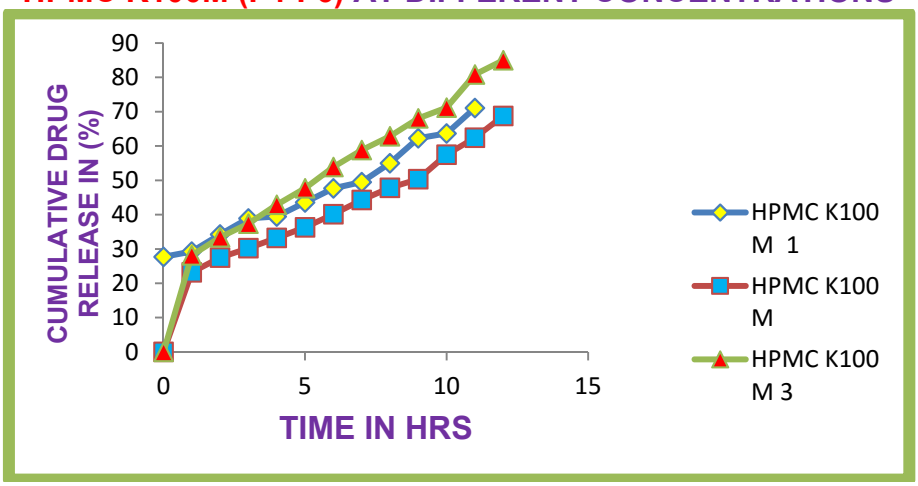


FIGURE 9C *IN* VITRO DRUG RELEASE PROFILE OF FEBUXOSTAT AND METHYL CELLULOSE (F7-F9) AT DIFFERENT CONCENTRATIONS

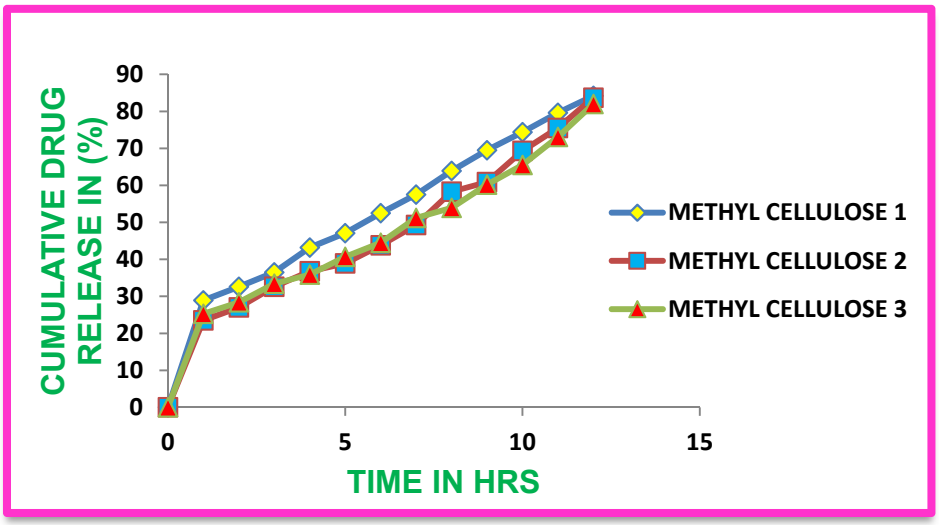


FIGURE 9D *IN* VITRO DRUG RELEASE PROFILE OF FEBUXOSTAT AND HPMC K4M AND EC (G1-G3) AT DIFFERENT CONCENTRATIONS

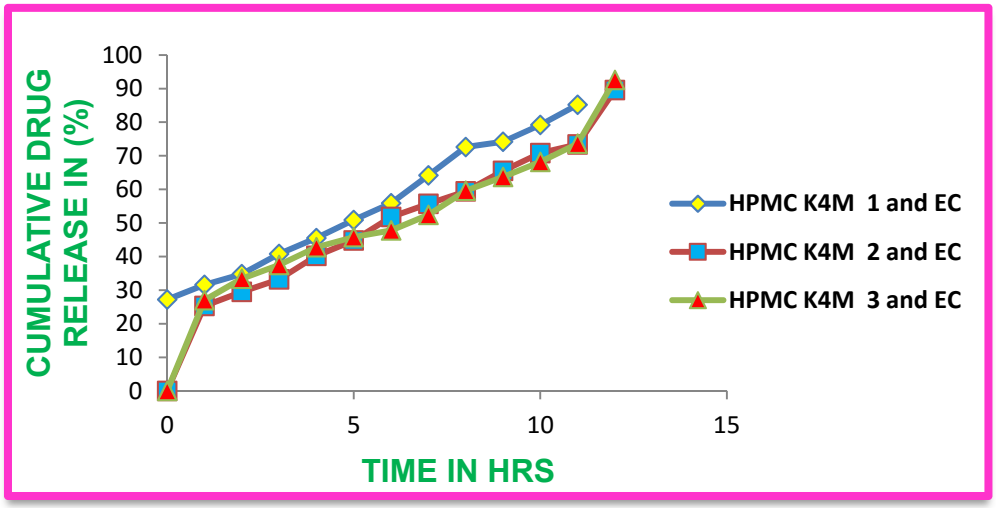


FIGURE 9E *IN* VITRO DRUG RELEASE PROFILE OF FEBUXOSTAT AND HPMC K100M AND EC (G4-G6) AT DIFFERENT CONCENTRATIONS

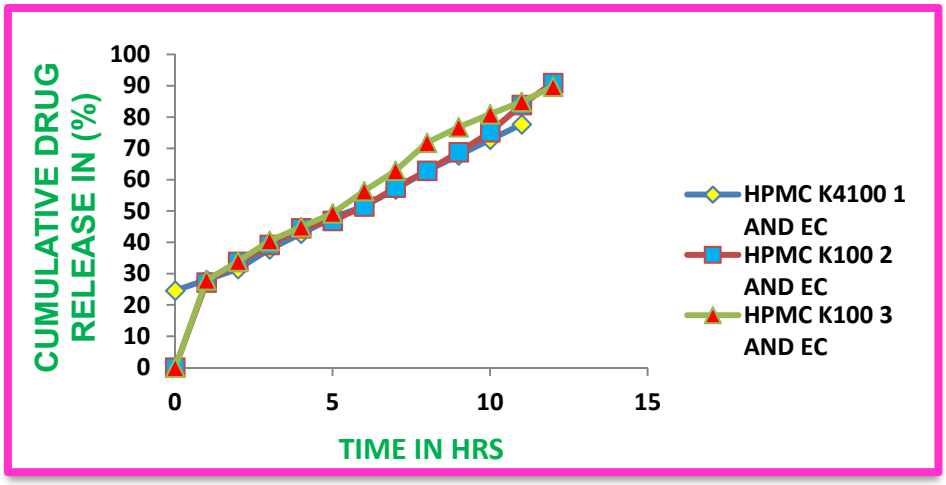


FIGURE 9F *IN* VITRO DRUG RELEASE PROFILE OF FEBUXOSTAT AND METHYL CELLULOSE AND EC (G7-G9) AT DIFFERENT CONCENTRATIONS

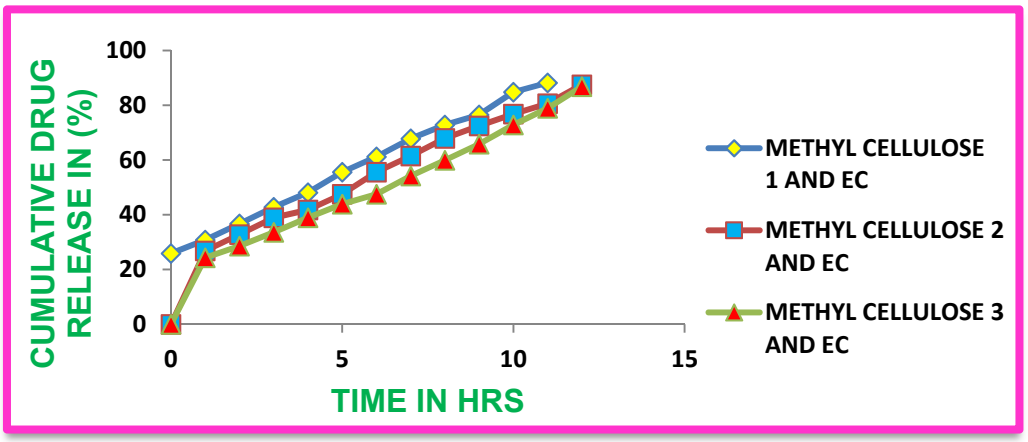


FIGURE 10A-1 COMPARISION OF *IN*VITRO ZERO ORDER RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K4M (F1-F3) AT DIFFERENT CONCENTRATIONS

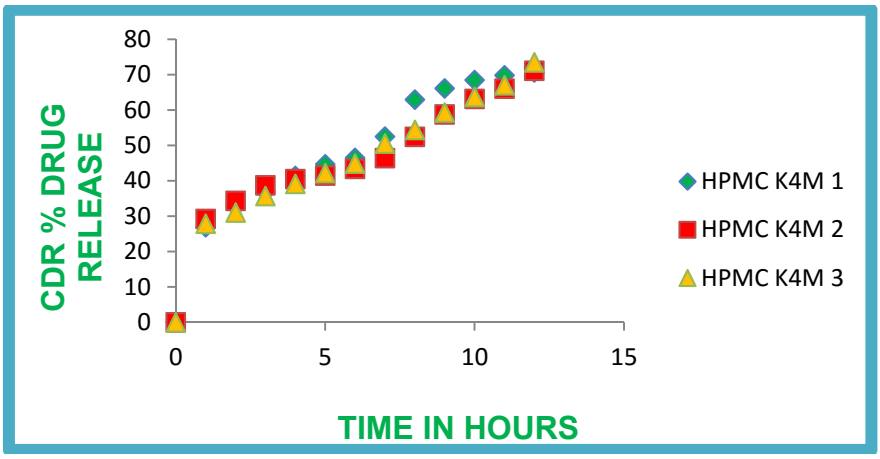


FIGURE 10A-2 COMPARISION OF *IN*VITRO ZERO ORDER RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K100M (F4-F6) AT DIFFERENT CONCENTRATIONS

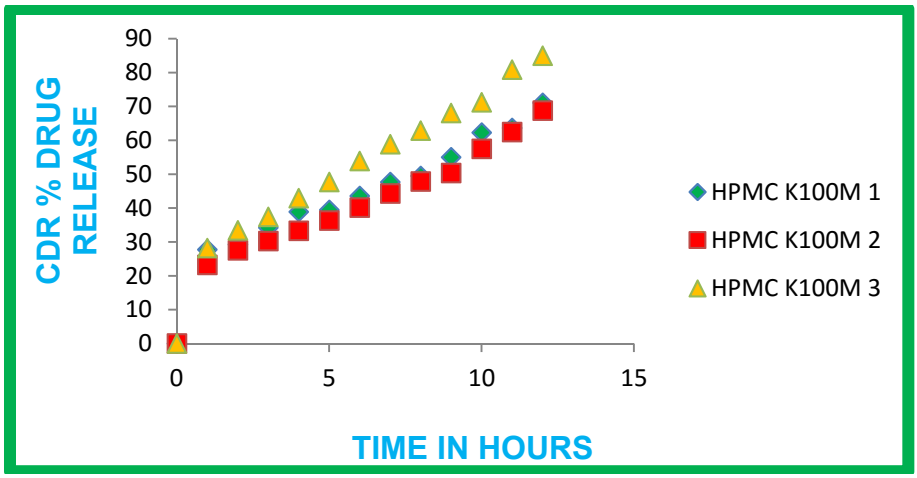


FIGURE 10A-3 COMPARISION OF *IN*VITRO ZERO ORDER RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND METHYL CELLULOSE (F7-F9) AT DIFFERENT CONCENTRATIONS

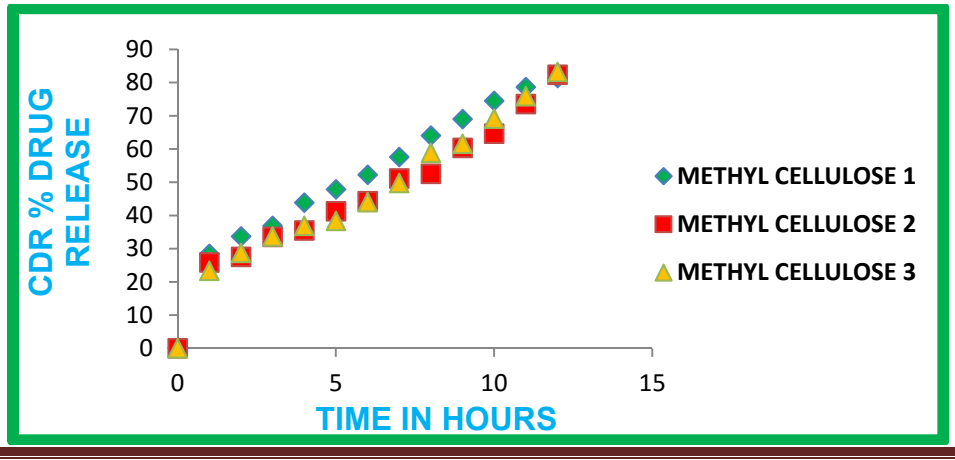


FIGURE 10A-4COMPARISION OF *IN*VITRO ZERO ORDER RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K4M AND EC (G1-G3) AT DIFFERENT CONCENTRATIONS

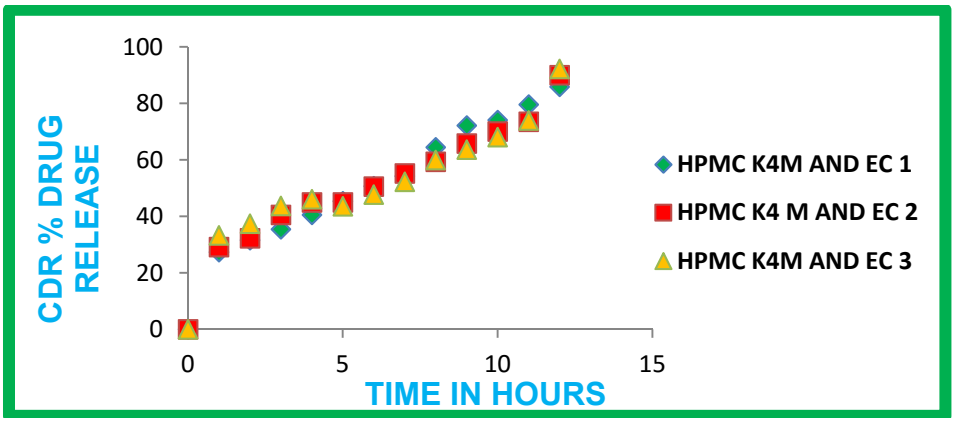


FIGURE 10A-5 COMPARISION OF *IN*VITRO ZERO ORDER RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K100M AND EC (G4-G6) AT DIFFERENT CONCENTRATIONS

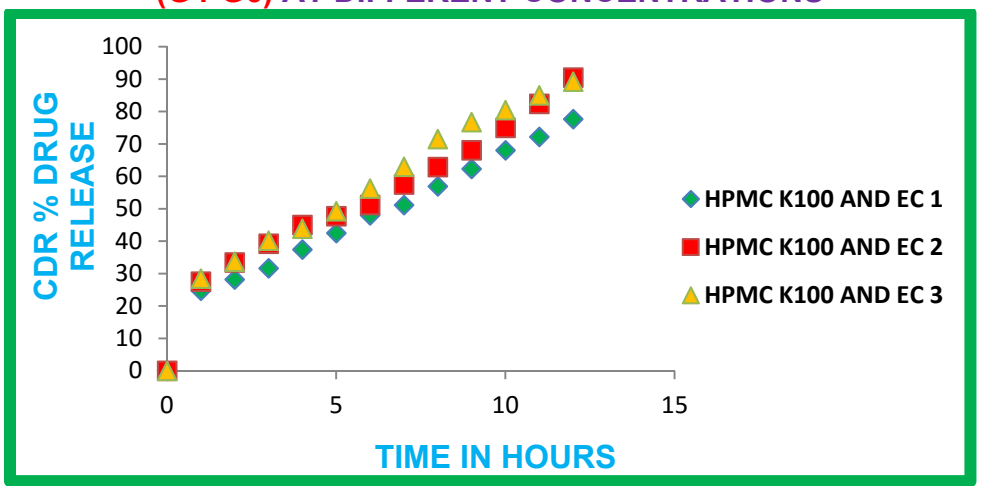


FIGURE 10A-6 COMPARISION OF *IN*VITRO ZERO ORDER RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND METHYL CELLULOSE AND EC (G7-G9) AT DIFFERENT CONCENTRATIONS

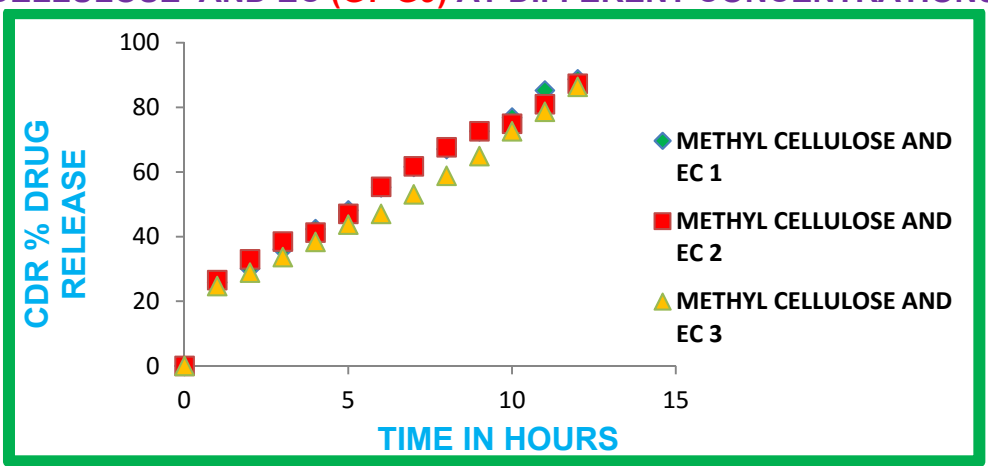


FIGURE 10B-1 COMPARISION OF *IN*VITRO FIRST ORDER RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K100M (F4-F6) AT DIFFERENT CONCENTRATIONS

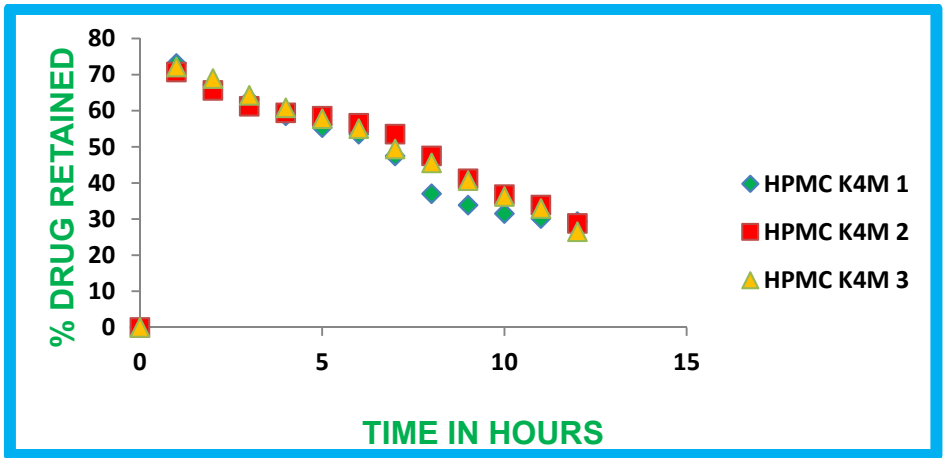


FIGURE 10B-2 COMPARISION OF *IN*VITRO FIRST ORDER RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K100M (F4-F6) AT DIFFERENT CONCENTRATIONS

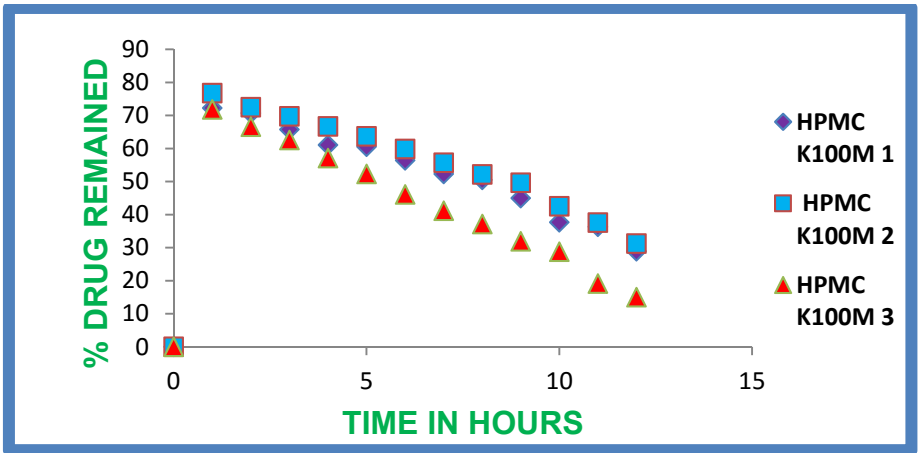


FIGURE 10 B-3 COMPARISION OF *IN*VITRO FIRST ORDER RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND METHYL CELLULOSE (F7-F9) AT DIFFERENT CONCENTRATIONS

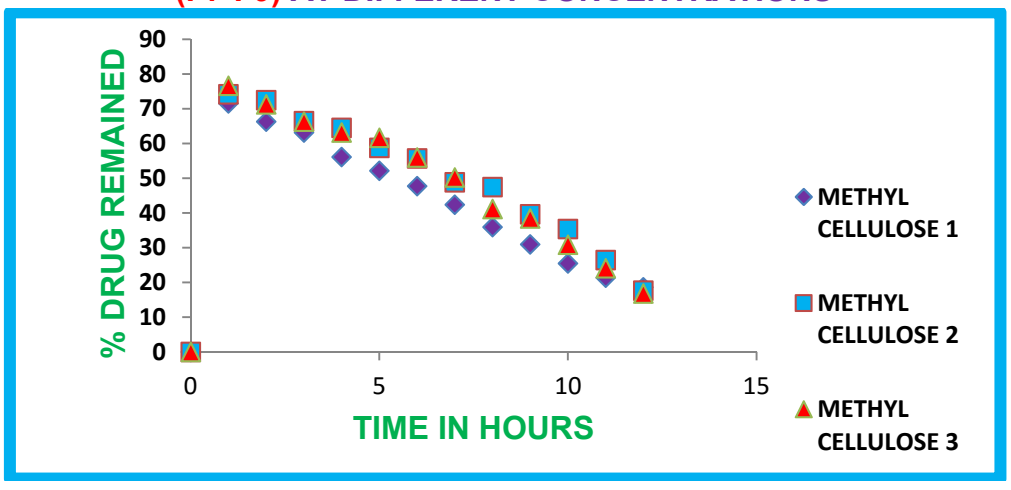


FIGURE 10B-4 COMPARISION OF *IN*VITRO FIRST ORDER RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K4M AND EC (G1-G3) AT DIFFERENT CONCENTRATIONS

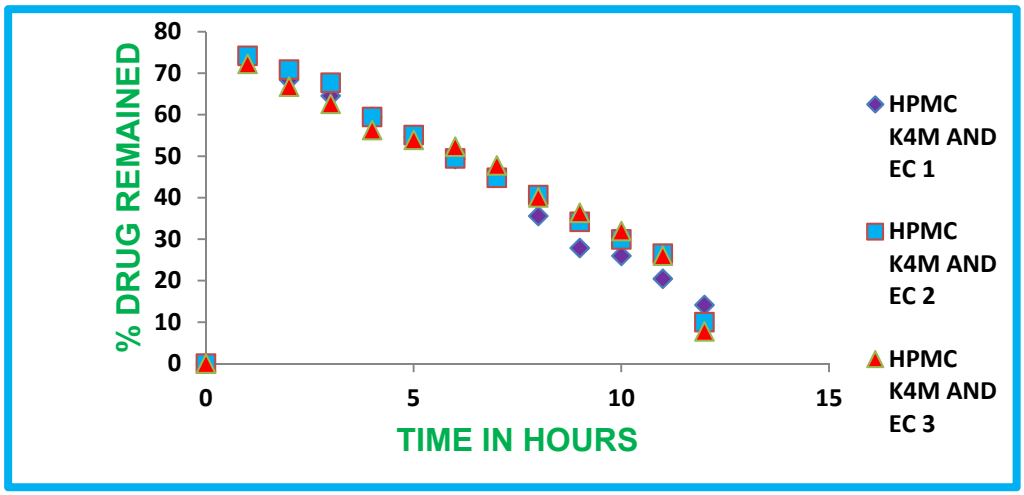


FIGURE 10B-5 COMPARISION OF *IN*VITRO FIRST ORDER RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K100M AND EC (G4-G6) AT DIFFERENT CONCENTRATIONS

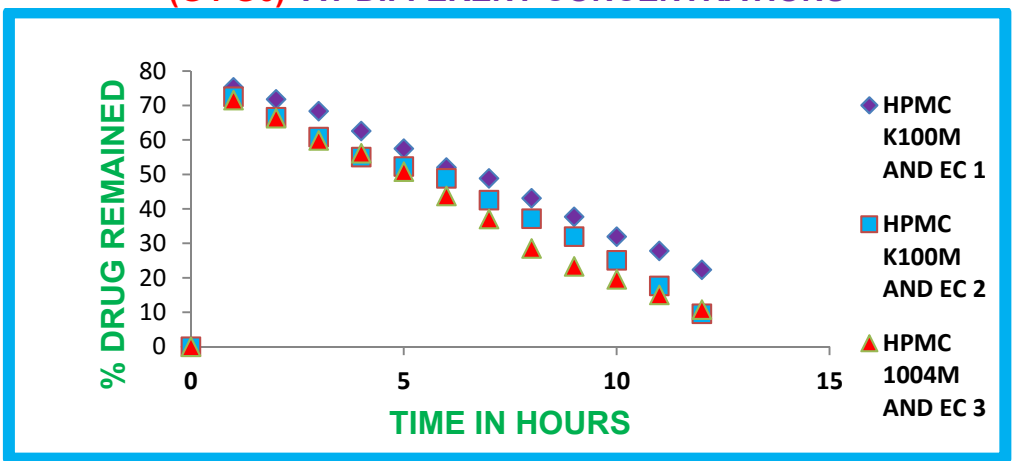


FIGURE 10B-6 COMPARISION OF *IN*VITRO FIRST ORDER RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND METHYL CELLULOSE AND EC (G7-G9) AT DIFFERENT CONCENTRATIONS

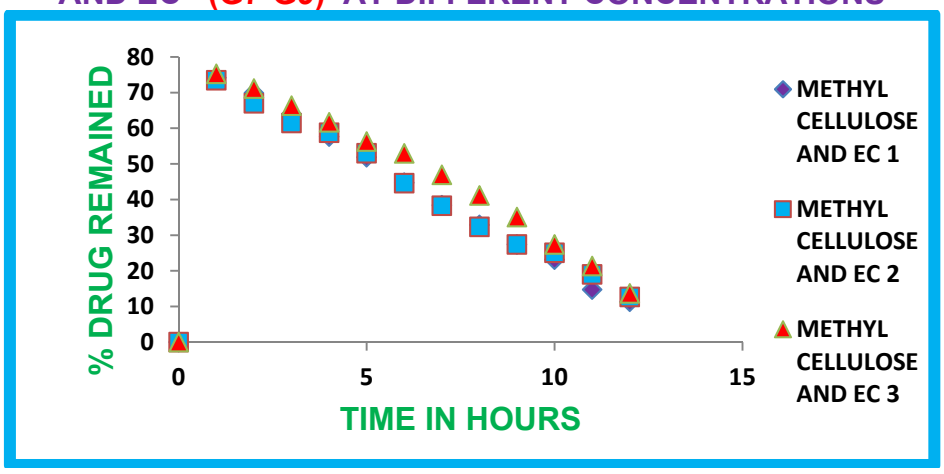


FIGURE 10C-1 COMPARISION OF *IN*VITRO HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K4M (F1-F3) AT DIFFERENT CONCENTRATIONS

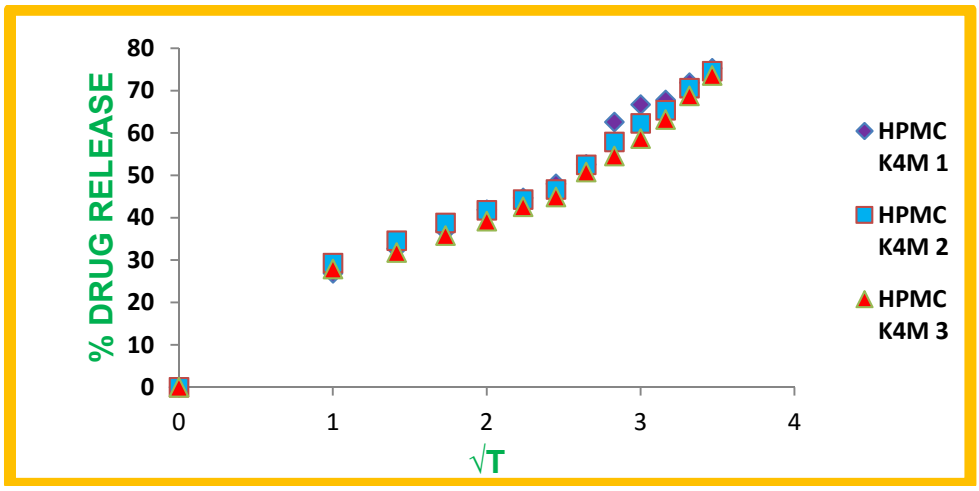


FIGURE 10C-2 COMPARISION OF *IN*VITRO HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K100M (F4-F6) AT DIFFERENT CONCENTRATIONS

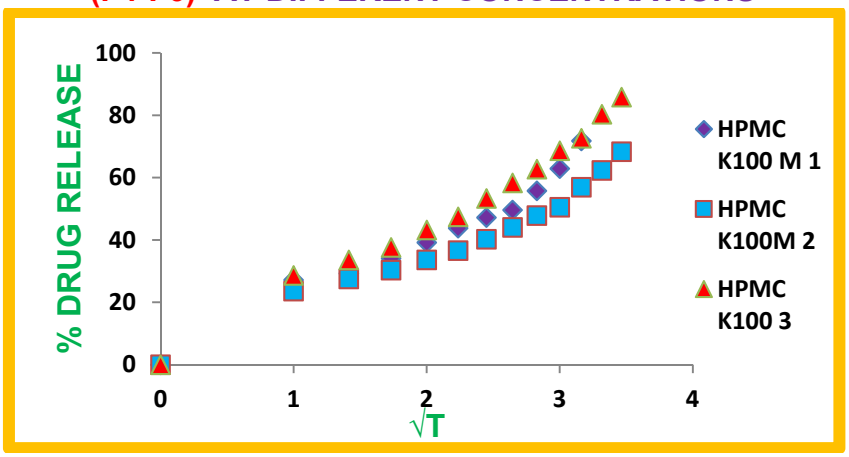


FIGURE 10C-3 COMPARISION OF *IN*VITRO HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND METHYL CELLULOSE (F7-F9) AT DIFFERENT CONCENTRATIONS

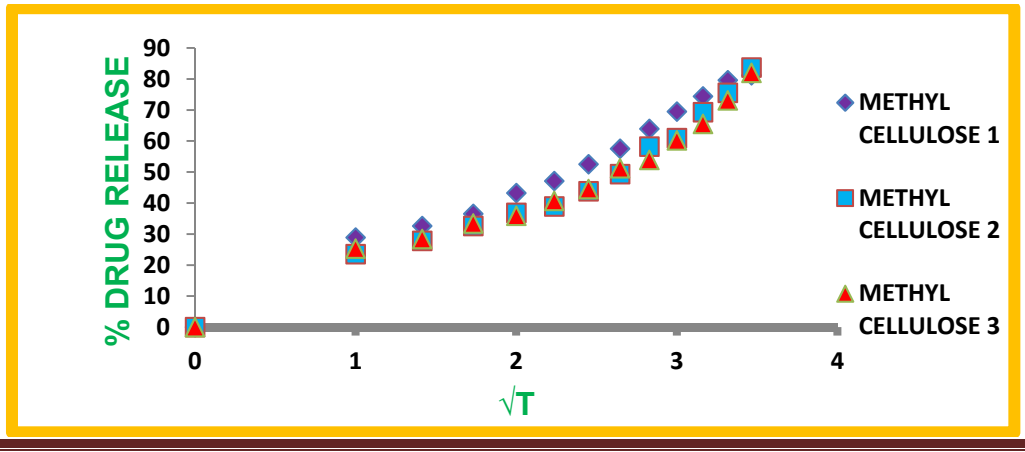


FIGURE 10C-4 COMPARISION OF *IN*VITRO HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K4M AND EC (G1-G3) AT DIFFERENT CONCENTRATIONS

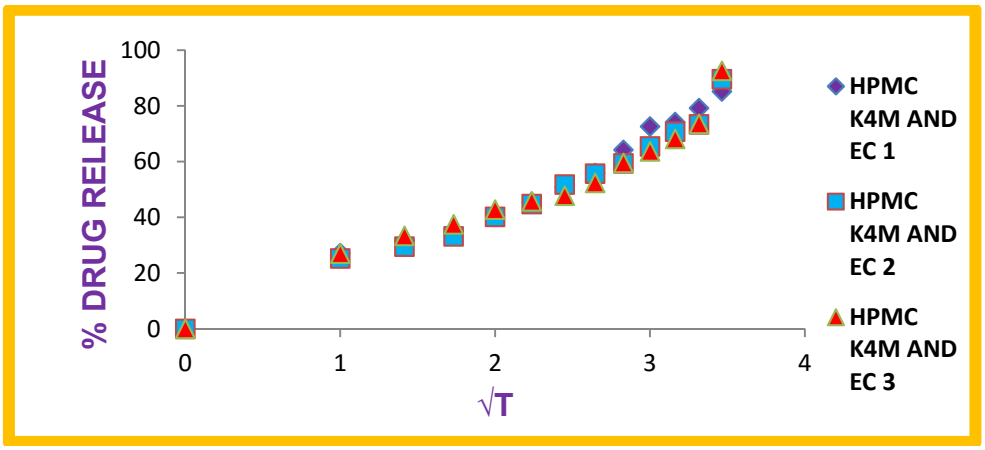


FIGURE 10C-5 COMPARISION OF *IN*VITRO HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K100M AND EC (G4-G6) AT DIFFERENT CONCENTRATIONS

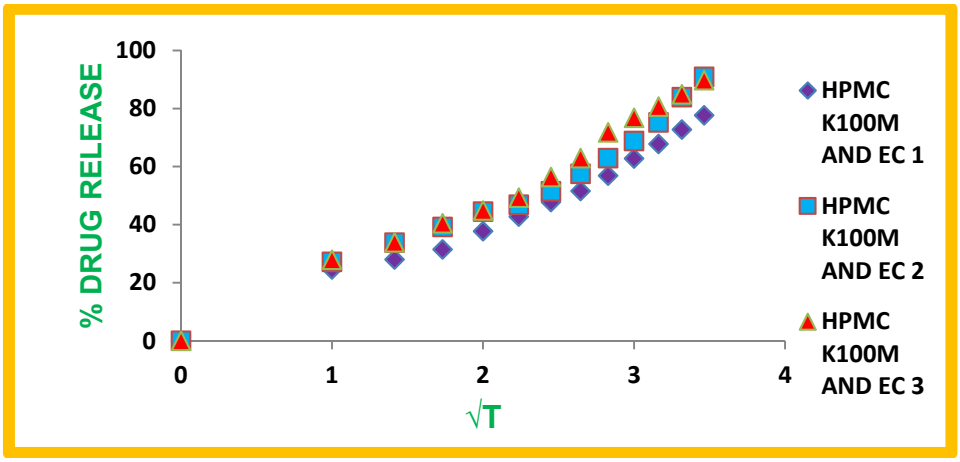


FIGURE 10C-6 COMPARISION OF *IN*VITRO HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND METHYL CELLULOSE AND EC (G7-G9) AT DIFFERENT CONCENTRATIONS

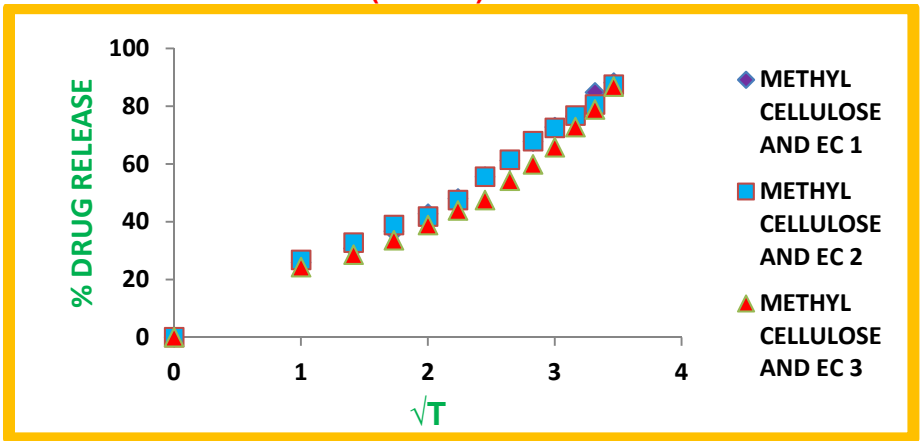


FIGURE 10D-1 COMPARISION OF *IN*VITRO KORESMEYER-PEPPAS MODEL RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K4M (F1-F3) AT DIFFERENT CONCENTRATIONS

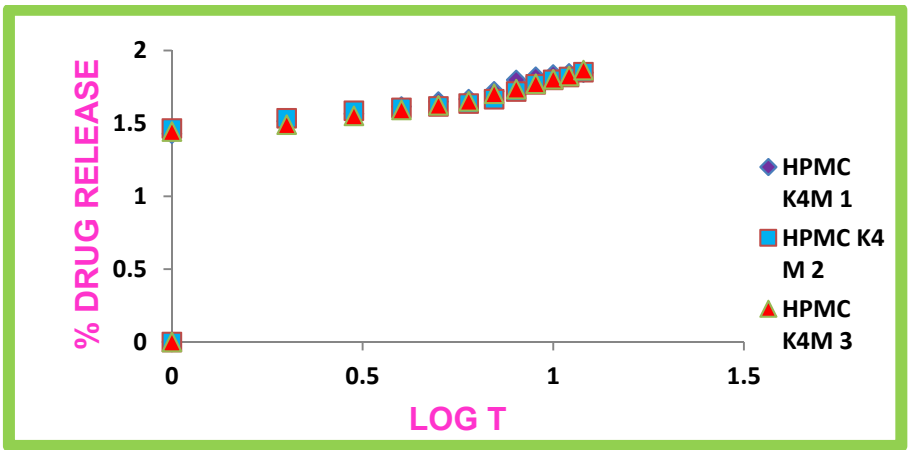


FIGURE 10D-2 COMPARISION OF *IN*VITRO KORESMEYER-PEPPAS MODEL RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K100M (F4-F6) AT DIFFERENT CONCENTRATIONS

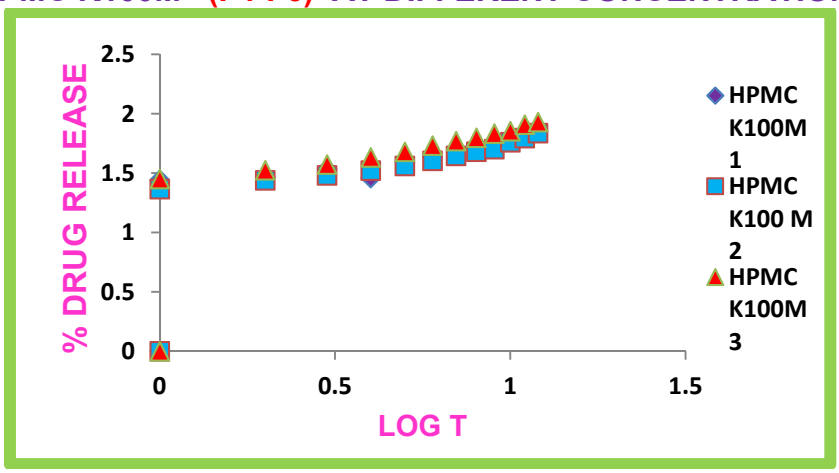


FIGURE 10D-3 COMPARISION OF *IN*VITRO KORESMEYER-PEPPAS MODEL RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND METHYL CELLULOSE (F7-F9) AT DIFFERENT CONCENTRATIONS

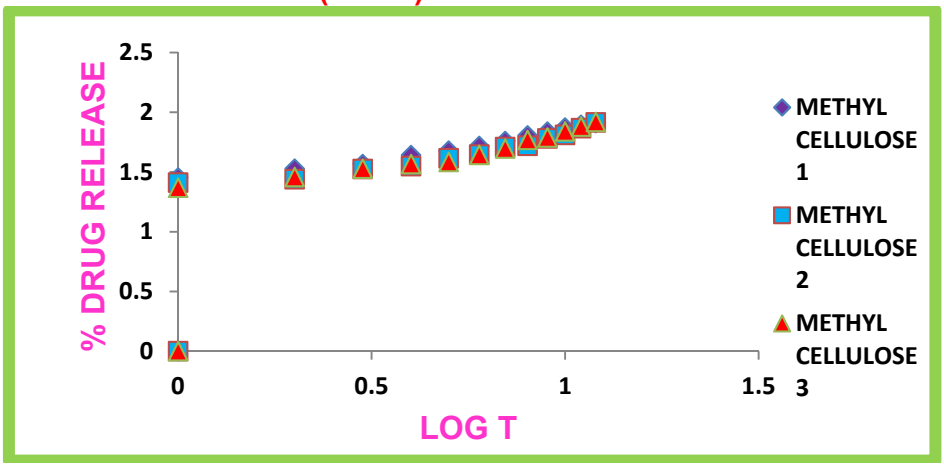


FIGURE 10D-4 COMPARISION OF *IN*VITRO KORESMEYER-PEPPAS MODEL RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K4M AND EC (G1-G3) AT DIFFERENT CONCENTRATIONS

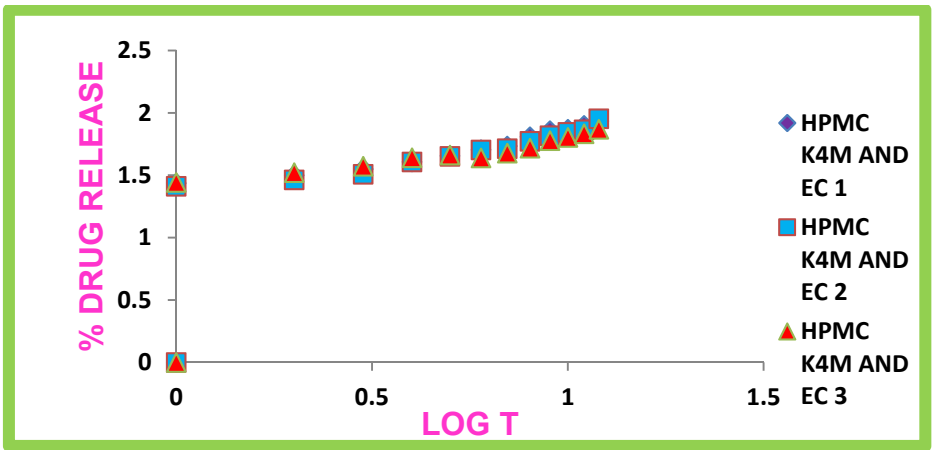


FIGURE 10D-5 COMPARISION OF *IN*VITRO KORESMEYER-PEPPAS MODEL RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K100M AND EC (G4-G6) AT DIFFERENT CONCENTRATIONS

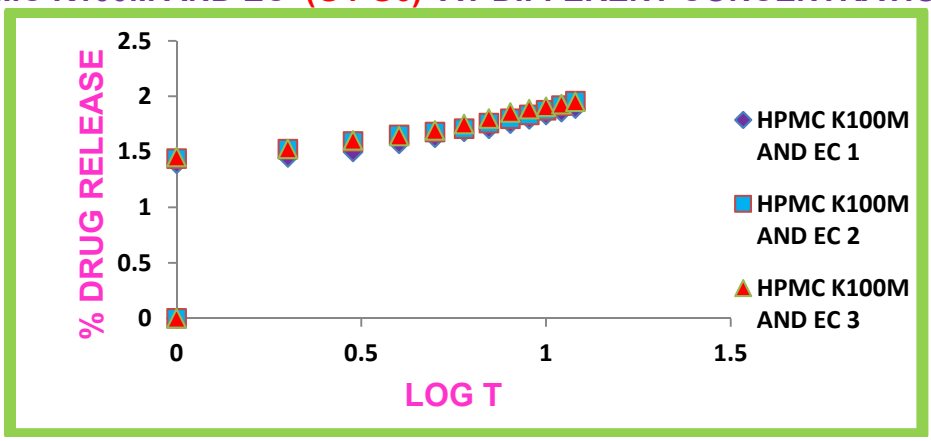


FIGURE 10D-6 COMPARISION OF *IN*VITRO KORESMEYER-PEPPAS MODEL RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND METHYL CELLULOSE AND EC (G7-G9) AT DIFFERENT CONCENTRATIONS

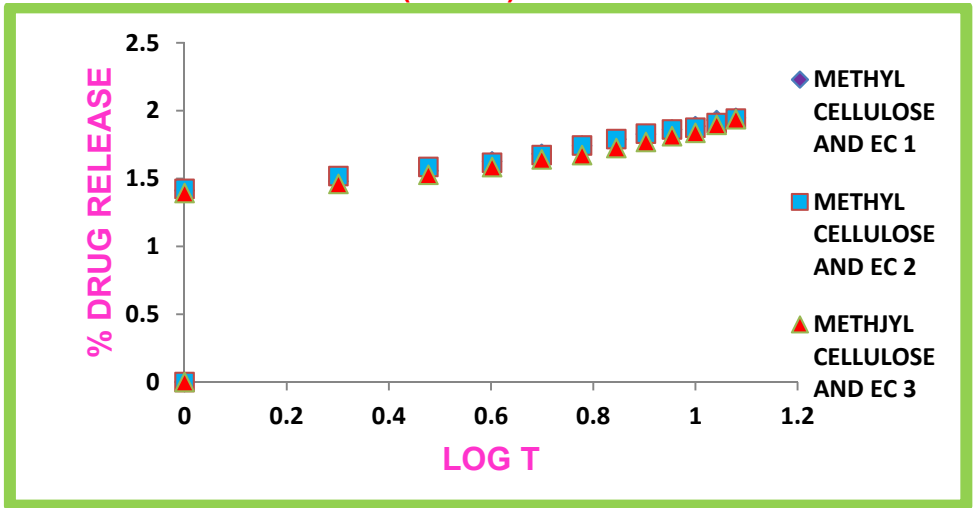


FIGURE 10E-1 COMPARISION OF *IN*VITRO HIXON-CROWELL MODEL RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K4M (F1-F3) AT DIFFERENT CONCENTRATIONS

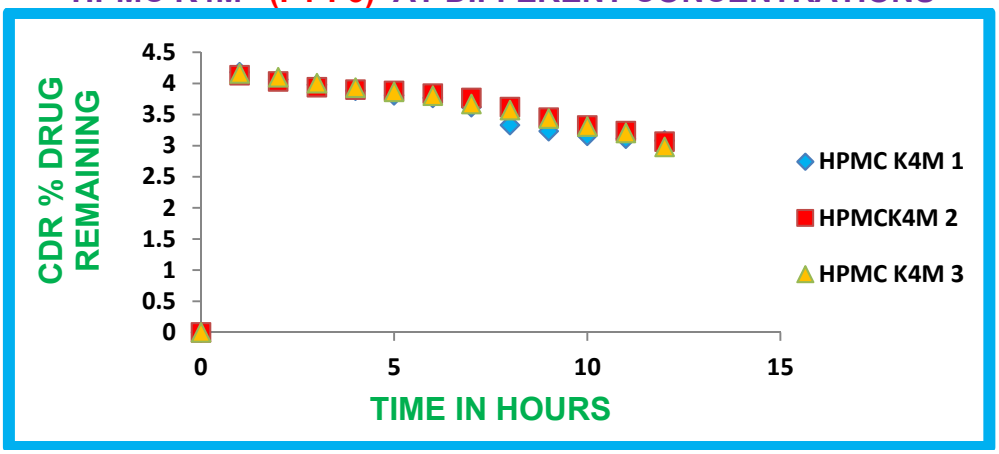


FIGURE 10E-2 COMPARISION OF *IN*VITRO HIXON-CROWELL MODEL RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K100M (F4-F6) AT DIFFERENT CONCENTRATIONS

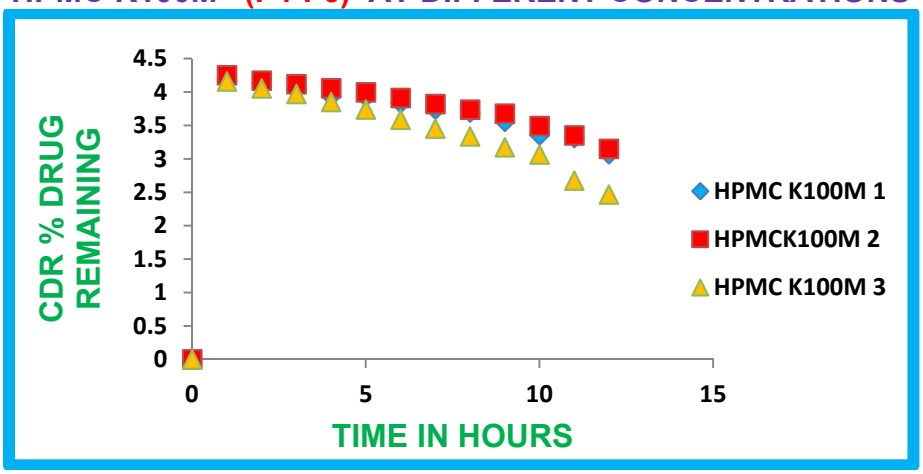


FIGURE 10E-3 COMPARISION OF *IN*VITRO HIXON-CROWELL MODEL RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND METHYL CELLULOSE (F7-F9) AT DIFFERENT CONCENTRATIONS

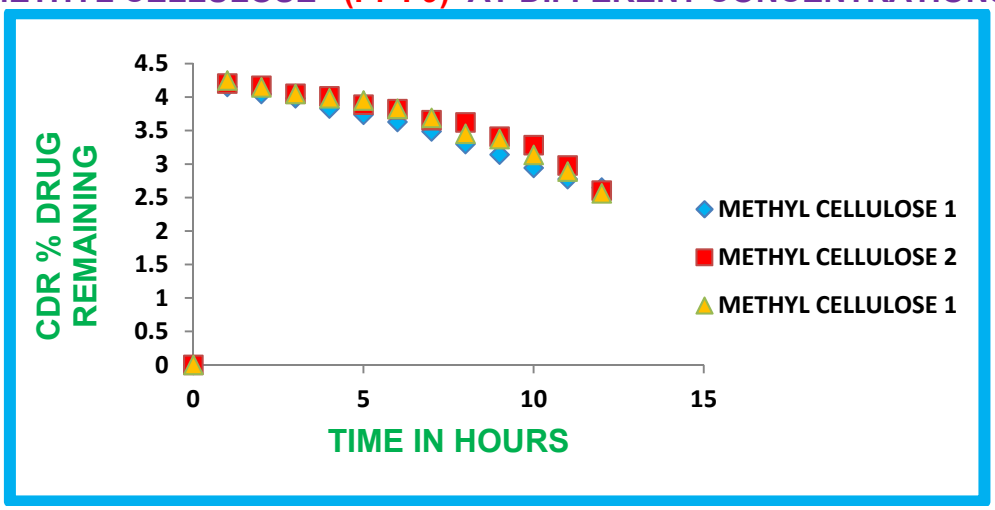


FIGURE 10E-4 COMPARISION OF *IN*VITRO HIXON-CROWELL MODEL RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K4M (G1-G3) AT DIFFERENT CONCENTRATIONS

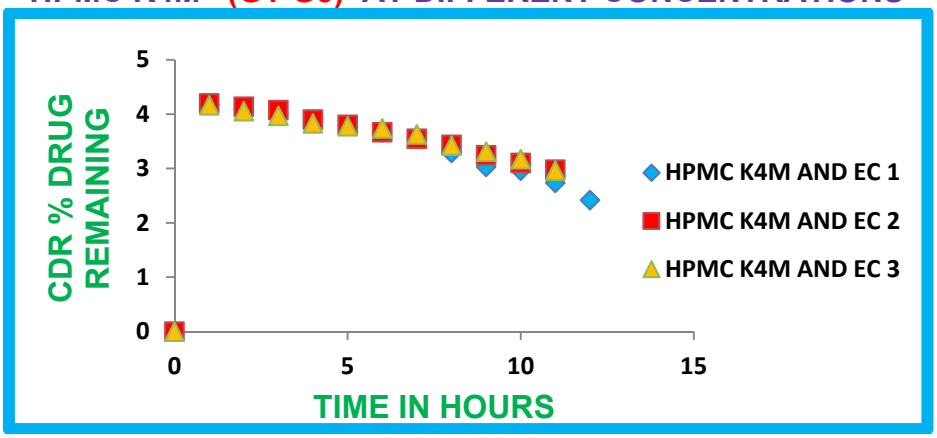


FIGURE 10E-5 COMPARISION OF *IN*VITRO HIXON-CROWELL MODEL RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND HPMC K100M (G4-G6) AT DIFFERENT CONCENTRATIONS

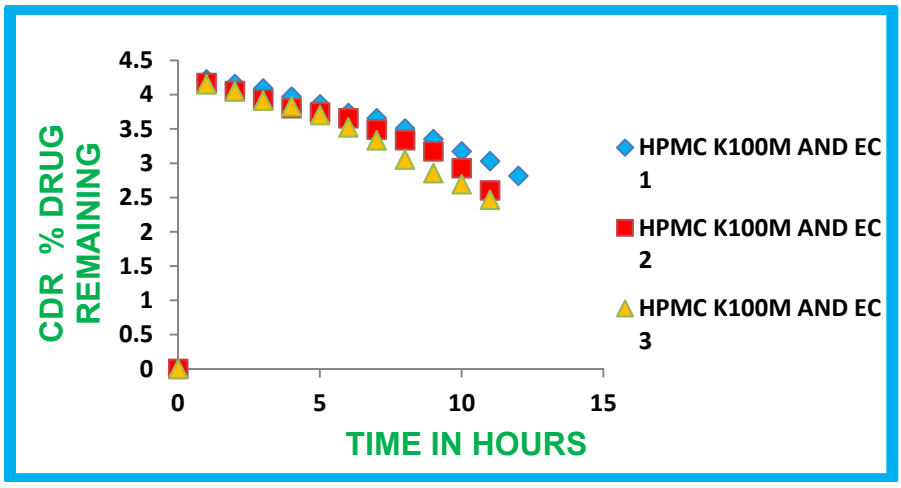


FIGURE 10E-6 COMPARISION OF *IN*VITRO HIXON-CROWELL MODEL RELEASE KINETICS OF FORMULATION CONTAINING FEBUXOSTAT AND METHYL CELLULOSE (G7-G9) AT DIFFERENT CONCENTRATIONS

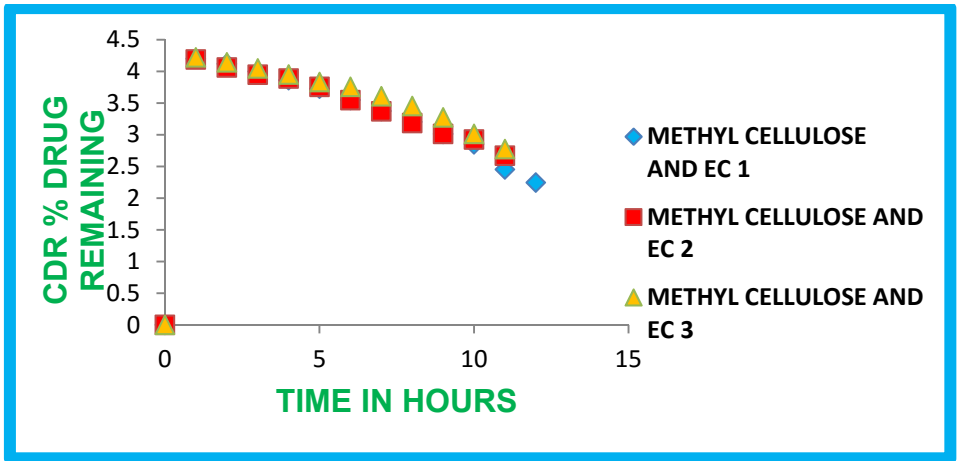


FIGURE 11: FTIR STUDY OF BEST FORMULATION (F5)

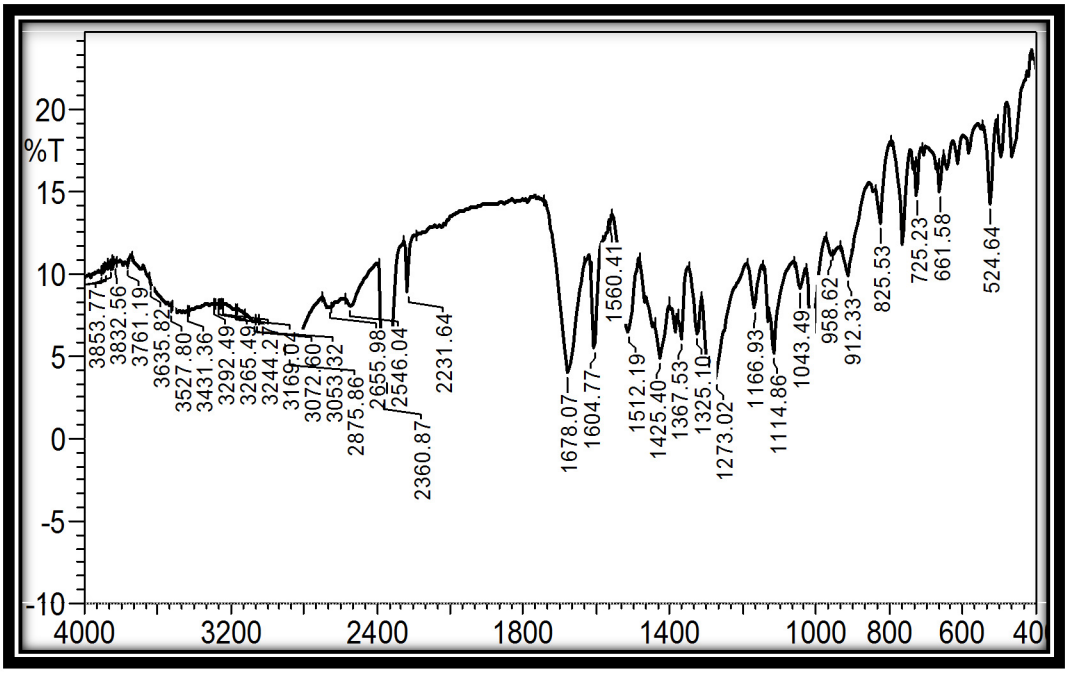


FIGURE 12: DSC THERMOGRAM OF BEST FORMULATION (F5)

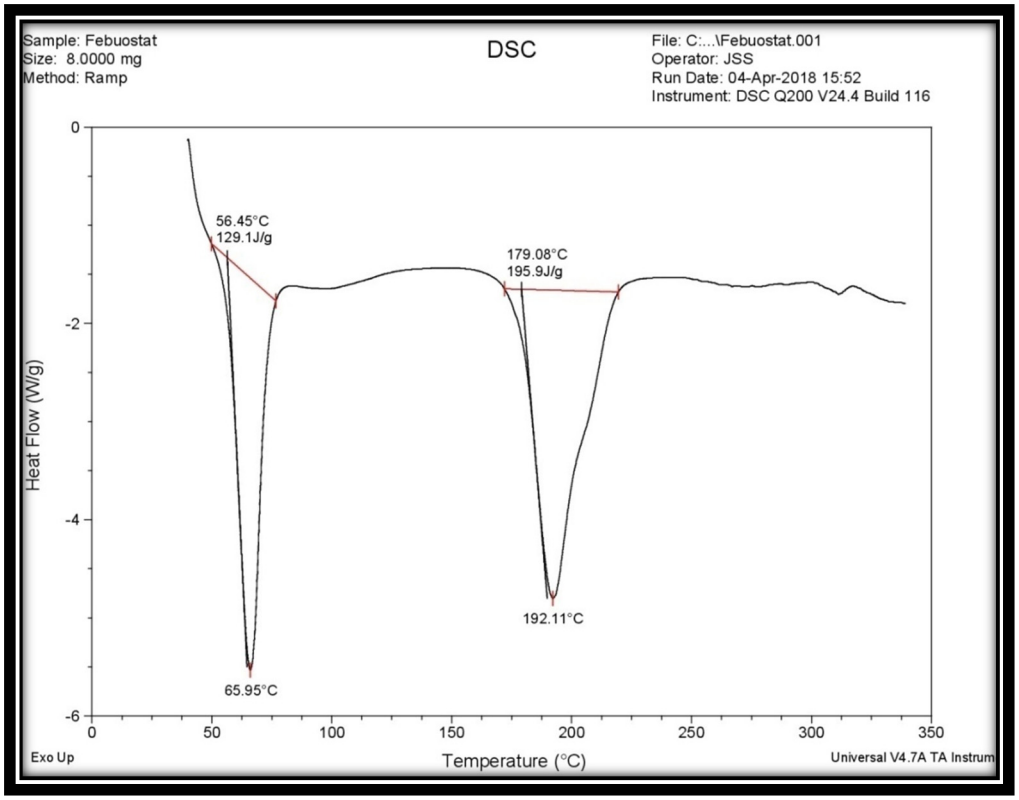


FIGURE13: PXRD PATTERNS OF BEST FORMULATION (F5)

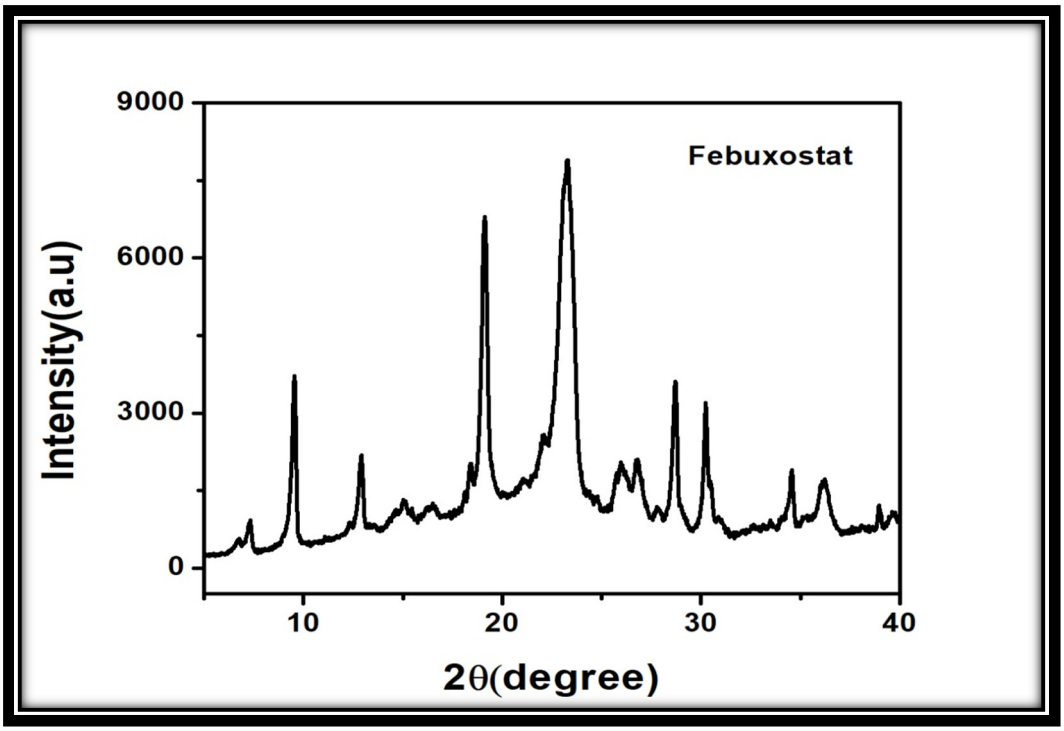


FIGURE 14: COMPARISION OF BEST FORMULATION WITH MARKETED FORMULATION

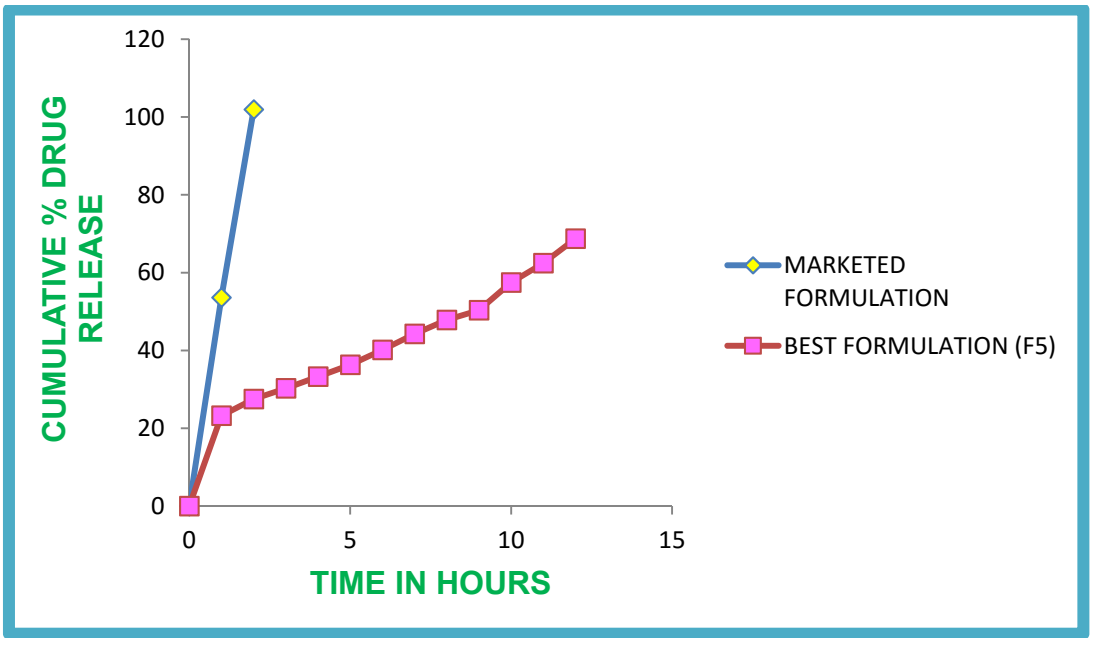
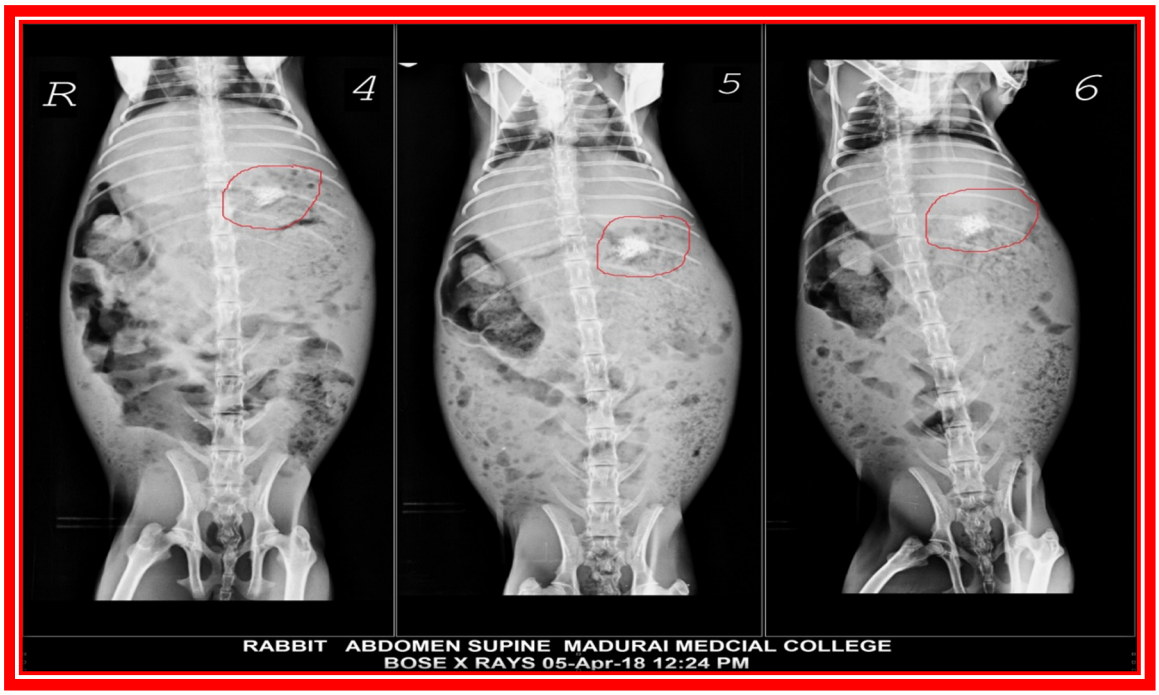


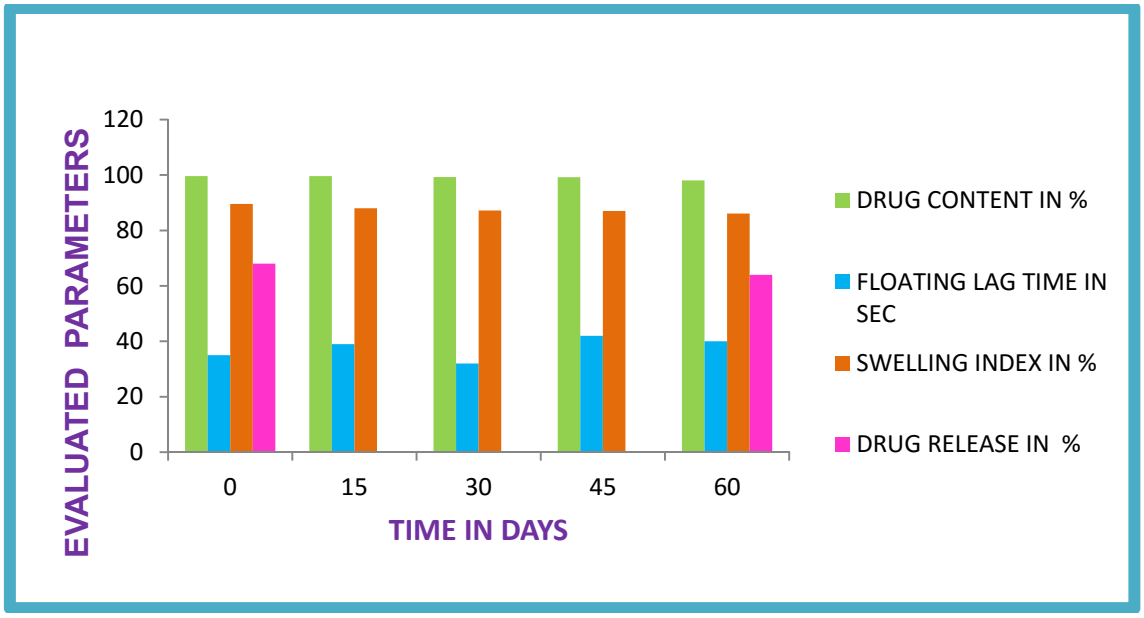
FIGURE 15: IN VIVO X-RAY STUDIES ON BEST FORMULATION (F5)

2ND HOUR 4TH HOUR 6TH HOUR



8TH HOUR 10TH HOUR 12TH HOUR

FIGURE 16: EVALUATION OF FEBUXOSTAT FLOATING SUSTAINED RELEASE MATRIX KEPT IN STABILITY AT 40^{0C}/75% RELATIVE HUMIDITY



CHAPTER 12

SUMMARY AND CONCLUSION

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SUMMARY:

- Floating drug delivery system offers a simple and practical approach to achieve increased **Gastric Residence Time(GRT)** and to modify drug release profiles essential for sustained, site specific and localized drug action.
- An attempt was made to formulate and evaluate floating drug delivery system containing **Febuxostat** as model drug by both Effervescent technique and non-effervescent techniques.
- The present work has aimed towards developing a floating drug delivery system of Febuxostat based on Novel approaches.
- It was hypothesized that a system that combines advantages of both floating and sustained release technology can be successful in the field of novel drug delivery system.
- The solubility of Febuxostat was enhanced by the melting method using PEG 6000 as a carrier.
- The λ_{max} of Febuxostat was found to be **317nm** in 0.1N HCl.
- The Febuxostat obeys the Beer's law within the concentration of **2 to 20µg/ml.**
- DSC and FT-IR studies indicated that there was no interaction between drug and excipients.

- The formulations **(F1 to F9)** were prepared by Effervescent technique and formulations **(G1 to G9)** were prepared by non- effervescent techniques using hydrophilic and hydrophobic polymers.
- The formulated tablets were analysed for Pre-compression and Post-compression parameters, *In vitro* release studies, release kinetics, *In vivo* x-ray studies, stability studies.
- The Pre-compression parameters of all the formulations were within the required limit that was suitable for formulation of the tablet.
- The Post-compression parameters, such as Hardness, Friability, Uniformity in weight and Drug content of all the formulated tablets were within the acceptable limits.
- The floating lag time and duration of buoyancy were found to be satisfied, for all the formulations.
- Among all, **formulation (F5)** was selected as best formulation based on *in-vitro* release studies, Swelling index and *in-vitro* buoyancy studies.
- The extent of drug release was found to be 68.34 in 12 hrs.
- The drug release model of all the formulations complies with the Zero-order kinetics followed by Non-Fickian diffusion mechanism.
- The ***in-vivo* X-Ray** study was performed for the best formulation.It shows the gastric residence time of more than 12 hrs.
- Selected formulation of Febuxostat was compared with marketed formulation.

CONCLUSION

- The results of the present study clearly indicate the feasibility to develop Febuxostat in the form of floating drug delivery system with prolongation of gastric retention time and controlled release.
- In my present study, the Effervescent formulations had better drug release, Floating Lag time, Swelling Index as compared to Non-Effervescent formulations.
- Increment in the concentration of swelling agent , decrement in the drug release. This may be due to increase in diffusion length of drug from dosage form to the dissolution studies.
- Increment in the concentration, of swelling agent, increment in Floating lag time, this may be due to gas generated by the gas generating agent was entangled between matrix formed by the swelling agent.
- Polymer swelling was crucial in determining the drug release rate and also important for floatation. The viscosity of the polymer had a major influence on swelling process and matrix integrity.
- Hydrophilic polymers induce the formation of strong viscous gel layer when they come in contact with the aqueous media that slowed down the rate of diffusion of medium into the tablet, which may result in the retardation or decrease in the drug release.
- The combination of hydrophilic and hydrophobic polymers, which restricts the penetration of dissolution medium inside the matrix, also restricts the formation of gel ,layer around the matrix.So, that the drug release from the hydrophobic matrix tablets gets decreased.

- Thus, I conclude that both the techniques are equally potential and contribute in the development of floating drug delivery systems.Both the techniques equally have their own merits and de-merits.The mechanism and action of drug, selection of polymers ,stability factors .,Trial experiments., etc decide the best suitable technique.
- The future studies may be extended to reveal the pharmacokinetic parameters related to bio-availability and clinical trial invesgtigations, that this type of formulations can be administered safely for the treatment of Chronic Gout with improved therapeutic efficacy.

CHAPTER

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